Inflammatory bowel disease and oral health: systematic review and a meta-analysis

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Abstract: BACKGROUND: The objective of this systematic review was to systematically investigate whether there is an association between inflammatory bowel disease (IBD) and oral health. METHODS: Literature searches for randomized and non-randomized studies were performed up to January 2017. Risk of bias within studies was assessed with the Downs and Black checklist. Across-studies risk of bias was assessed with the GRADE framework. Quantitative synthesis was conducted with random-effects meta-analyses. RESULTS: A total of 9 cross-sectional studies including 1297 patients were included. IBD was associated with increased risk of periodontitis (332 more patients per 1000 patients; 95% confidence interval (CI): 257-388 patients; $p < 0.001$) compared to non-IBD patients. Additionally, the Decayed-Missing-Filled-Teeth index of IBD patients was significantly worse than non-IBD patients (mean difference: 3.85; 95% CI: 2.36-5.34; $p = 0.005$). Patients with ulcerative colitis had considerably worse oral health for most of the assessed factors, while the quality of overall evidence ranged from high to low, due to the observational nature of contributing studies. CONCLUSIONS: Inflammatory bowel disease was associated with significantly higher risk of periodontitis and worse oral health compared to non-IBD patients. However, longitudinal studies are needed in order to establish a causality link between IBD and periodontal disease.

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Title Page

Inflammatory bowel disease and oral health: systematic review and a meta-analysis

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Clinical Relevance

Scientific rationale for study: A number of systematic diseases including cardiovascular disease, diabetes, metabolic syndrome and obesity have been associated with periodontal disease.

Principal findings: According to existing evidence from the literature, inflammatory bowel disease seems to be associated with increased risk of periodontal disease and increased caries experience, although this needs to be confirmed by further studies.

Practical implications: Evidence from this systematic review could guide future longitudingal studies with large sample sizes and more rigorous methodology, and help guide the clinical management of patients with inflammatory bowel disease.

Abstract

Background: The objective of this systematic review was to systematically investigate whether there is an association between inflammatory bowel disease (IBD) and oral health.

Methods: Literature searches for randomized and non-randomized studies were performed up to January 2017. Risk of bias within studies was assessed with the Downs and Black checklist. Across-studies risk of bias was assessed with the GRADE framework. Quantitative synthesis was conducted with random-effects meta-analyses.

Results: A total of 9 cross-sectional studies including 1 297 patients were included. IBD was associated with increased risk of periodontitis (332 more patients per 1 000 patients; 95% confidence interval: 257 to 388 patients; $p<0.001$) compared to non-IBD patients. Additionally, the Decayed-Missing-Filled-Teeth index of IBD patients was significantly worse than non-IBD patients (mean difference: 3.85; 95% CI: 2.36 to 5.34; $p=0.005$). Patients with ulcerative colitis had considerably worse oral health for most of the assessed factors, while the quality of overall evidence ranged from high to low, due to observational nature of contributing studies.

Conclusions: IBD was associated with significantly higher risk of periodontitis and worse oral health compared to non-IBD patients. However, longitudinal studies are needed in order to establish a causality link between IBD and periodontal disease.

Registration: CRD42015019436

Introduction

Rationale

Inflammatory bowel disease (IBD) and its two major disorders, Crohn's Disease (CD) and Ulcerative Colitis (CD), are a significant problem across the world, affecting about one in 200 people in developed countries and having a rising incidence and prevalence in developing countries (Molodecky et al. 2012). IBD is associated with many debilitating symptoms, including urgent diarrhoea, rectal bleeding, vomiting, anorexia, and lethargy, which frequently lead to poor psychosocial wellbeing with extensive consequences (Neovius et al. 2013). The financial burden of IBD for the healthcare system is considerable, with more than 2.2 billion US/year in the USA alone (Everhart & Ruhl 2009). The development and progression of IBD is considered to be based on a complex combination of genetic influences and environmental factors (Ellinghaus et al. 2015), where disturbed host-microbiome interactions likely play a significant part (Jostins et al. 2012).

Several of these IBD-relevant factors and influences are also risk factors for periodontitis (Brandtzaeg 2001, Kinane & Bartold 2007, Indriolo et al. 2011). In addition, studies have shown that the progression of disease in both IBD and periodontitis is characterized by immunoinflammatory processes and tissue destruction (Brandtzaeg 2001, Kinane & Bartold 2007). Finally, several other oral manifestations of IBD have been reported in the last decades, including oral soft-tissue lesions, cobblestoning, aphthous ulcers, lymphadenopathy, and pyostomatitis (Dudeney 1969, Chan et al. 1991, Scheper & Brand 2002, Harty et al. 2005).

To this end, periodontitis has been associated with a number of systemic diseases and conditions including diabetes, metabolic disorder, and obesity (Chaffee & Weston 2010, Suvan et al. 2011, Nibali et al. 2013, Papageorgiou et al. 2015a). However, to our knowledge the possible association between IBD and periodontitis has not yet been adequately assessed in an evidence-based manner. Such evidence could identify similarities between the two entities that aid in the elucidation of the underlying biological principles of IBD and its forms, as well as provide information about an increased global burden of care for periodontal disease (Petersen & Ogawa 2012) in IBD patients.

Objectives

The primary aim of this systematic review was to investigate whether the prevalence of periodontal disease is higher in patients with IBD compared to IBD-free patients, with the main research question being: "Do IBD patients have the same prevalence of periodontal disease as IBD-free patients?". The secondary aim was to assess whether IBD is associated with other parameters of oral health.

Methods

Protocol and Registration

The protocol for this systematic review was made *a priori*, agreed upon from all authors and registered in PROSPERO (CRD42015019436). This systematic review is conducted according to the Cochrane Handbook (Higgins & Green 2011) and reported according to the PRISMA statement (Liberati et al. 2009) and its extension for abstracts (Beller et al. 2013).

Eligibility Criteria

Inclusion and exclusion criteria were determined *a priori* (Appendix A). Both randomized controlled studies (RCTs) and non-RCTs that assessed any of the pre-specified periodontal or oral health outcomes in patients with and without IBD were included.

Information Sources and Search

Electronic general, open access, regional and grey literature databases were systematically searched up to January 2017 (Appendix B). MESH terms and relative keywords were used accordingly for each electronic database. No limitations were applied regarding publication year and status or language. The reference lists of included articles and relevant reviews were manually searched. Grey literature was searched through appropriate databases and registers. Authors were contacted when necessary for additional data or clarifications.

Study Selection

A study was judged as eligible, when none of the exclusion and all of the inclusion criteria were fulfilled. After removal of duplicates, articles were screened on the basis of title, abstract, and full-text. When the decision on the basis of title and abstract was inconclusive, the full-text article was acquired. Additional reports of the same trial/cohort were grouped together. When an identical study was published in more than one language, the most complete report was preferred, irrespective of language. Study selection was initially conducted by one author (SNP), who screened the titles and/or abstracts of retrieved studies. Subsequently, the full texts of potentially eligible studies (and from those abstracts which did not provide sufficient information to include/exclude) were screened by two authors independently (SNP and MH). Differences between the two authors were settled by a third author (JD).

Data Collection Process and Data Items

Data extraction was performed independently by the same two review authors (SNP and MH) in a pre-defined and piloted collection form. Any disagreement was resolved by discussion with a third author (JD). Outcomes to be included were specified *a priori* at the protocol stage. All given post-treatment timepoints were to be included, but no such data existed.

Risk of Bias in Individual Studies

The risk of bias of RCTs was to be assessed with the Cochrane Collaboration's tool (Higgins & Green 2011), but no RCTs were identified. The risk of bias of non-RCTs was assessed with a modified version of the Downs & Black (1998) checklist.

Summary Measures and Synthesis of Results

Data were summarized and considered suitable for pooling, if similar disease groups were reported (or could be formed) and the same outcomes were reported. In cases of inadequate reporting, the missing data were calculated or requested from the authors. Data reported as medians and interquartile ranges were converted to means and standard deviations. If studies reported data for CD and UC, but not for IBD collectively, data were pooled prior to the meta-analysis (Higgins & Green 2011).

Mean differences (MD) for continuous outcomes and Odds Ratios (ORs) for binary outcomes, together with their corresponding 95% confidence intervals (CI) were calculated. A random-effects model as proposed by DerSimonian & Laird (1986) was chosen *a priori* as the primary method to estimate all pooled estimates, since clinical heterogeneity was expected (Papageorgiou 2014). The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots for the localization of heterogeneity, by calculating the tau^2 and the I^2 statistic, respectively, and assessing the magnitude and direction of heterogeneity. The 95% CIs around I^2 were calculated according to the non-central χ^2 approximation of Q. In case of considerable unexplained heterogeneity ($I^2 > 75\%$) attempts were made to achieve homogeneity and, if they failed, meta-analysis was omitted. For meta-analyses with ≥ 3 trials, 95% prediction intervals (PrI) (Higgins et al. 2009) were calculated to predict effects in a future clinical setting. These incorporate observed heterogeneity in the meta-analysis estimates and provide a range of possible results that could exist in a future clinical setting. All analyses were performed in Stata version 12 (StataCorp LP, College Station, TX) with the macros metan,

heterogi, and metareg. All p values were 2-sided with α set at 5%, except for the test of heterogeneity, where α was set at 10%. No adjustment in the significance level was adopted to control for increased Type I error, since the nature of meta-analysis is observational *per se* and aims to identify existing significant associations.

Risk of Bias Across Studies & Additional Analyses

The overall quality of evidence (confidence in effect estimates) for each of the main outcomes was rated using the GRADE approach (Guyatt et al. 2011). For this assessment, the risk of bias of each included trial was re-assessed separately at outcome level. The minimal clinical important, large, and very large effects for continuous outcomes were conventionally defined (Sloan et al. 2006) as half, one, and two standard deviations, respectively (and as 1.5, 2.5, and 4.3 for the odds ratio). The standard deviation for an outcome was averaged from the existing trials. The produced forest plots were augmented with contours denoting the magnitude of the observed effects. Finally, the optimal information size (i.e. required meta-analysis sample size) was calculated for each outcome independently for $\alpha = 5\%$ and $\beta = 20\%$.

Random-effects meta-regressions were conducted for the comparison of IBD compared to healthy patients according to the following characteristics of IBD patients (a) mean age, (b) gender (assessed through the male/female ratio), (c) smoking (percentage of patients smoking), (d) IBD activity (percentage of patients with active disease), and (e) medication use, when at least 3 studies were included. Small study effects and signs of publication bias were planned to be assessed, if at least ten studies contributed to the meta-analyses. Sensitivity analyses were planned to be conducted to check the results' robustness according to follow-up, error of the method, definition of periodontitis, design of included studies (Papageorgiou et al. 2014a, Papageorgiou et al. 2015b), and improvement of the GRADE assessment.

Results

Study Selection

A total of 362 and 4 papers were identified through the electronic (Appendix C) and manual searches, respectively (Fig. 1). After removal of duplicates and initial screening, 43 papers were judged against the eligibility criteria, leaving a final number of 14 included papers (Fig. 1; Appendix C; Table 1). Six publications (Barro 2007, Barros et al. 2008, Brito et al. 2008, Silva 2008, Figueredo et al. 2011, Brito et al. 2013), referring to the same study and its follow-ups, were grouped, leaving a total of 9 unique studies that were finally included.

Study Characteristics

The characteristics of the included studies are shown in Table 1. Eight case-control studies from different countries were included with a total of 744 IBD patients and 553 healthy individuals. Among the IBD patients described in the included studies 379 of them (56%) had CD and 300 (44%) had UC. In the studies that reported demographic characteristics, the male/female patient distribution was balanced in the IBD and healthy groups (45% to 51% in the IBD and 45% to 54% in the healthy group). Likewise, the mean age across studies was balanced between the IBD and healthy groups (37.2 and 35.7 years).

Methodological Adequacy (Risk of Bias) of Individual Studies

The risk of bias assessment for the included studies can be seen in Table 2. Serious methodological inadequacies that could be associated with bias were found in four studies for at least one methodological domain. Most problematic domains were the use of periodontal status as a criterion for patient enrollment in the study and incomplete reporting of patient characteristics or statistical analyses.

Results of Individual Studies and Data Synthesis

The results of the individual studies that were not included in the meta-analyses can be found in Appendix D. The performed meta-analysis comparing IBD patients with healthy patients overall, CD patients with healthy patients, and UC patients with healthy patients are shown in Tables 3-4, Fig. 2, and Appendix E–H. Compared to healthy patients, patients with IBD were significantly more likely to have periodontitis (Fig. 2), had significantly higher % of sites with large clinical attachement loss (3 to 5 mm) higher mean pocket probing depth, higher periodontal treatment need, higher DMFT index, and more oral lesions. Patients with CD, likewise, were significantly more likely to have periodontitis, had significantly higher DMFT index, and significantly higher percentage of sites with pocket probing depth >3mm (Appendix G). Finally, patients with UC were significantly more likely to have periodontitis or oral lesions, had significantly fewer teeth (Appendix E), greater DMFT index (Appendix F), greater percentage of sites with clinical attachment loss >3mm, and greater pocket probing depth (Appendix H).

Risk of Bias Across Studies

The risk of bias across studies (quality of evidence) according to the GRADE approach is summarized in Table 4 and Appendix I.

As far as the primary outcome of this review, prevalence of periodontitis, is concerned, high quality evidence supported the association of IBD generally (or CD and UC separately) with increased risk of periodontitis. IBD was associated with a higher risk of periodontitis by 332 patients per 1000 compared to healthy patients. The numbers-needed-to-treat indicated that for every 3 or 4 patients screened, an additional patient with periodontitis would be identified, if these patients had IBD. The subtype of IBD (CD or UC) had also a distinct effect on oral health, with UC patients being more severely affected compared to CD patients (additional increase in risk by 42 per 1000 patients).

As far as the two secondary outcomes of number of teeth and DMFT index of patient were concerned, low quality evidence indicated that IBD was associated with fewer teeth per patient and higher DMFT index. The only reason for the low GRADE score was the fact that it was based on observational non-experimenal studies that provided only a snapshot picture of the disease. Patients with IBD (either CD or UC) had an average of one tooth less (p=0.090) and a greater DMFT index by 3.85 (p=0.005). Likewise, to the prevalence of periodontitis, both the number of teeth and the DMFT index were more severely affected in UC patients than in CD patients compared to healthy patients (Appendix G and H). This was also seen in an explorative post-hoc comparison between UC and CD patients, where UC patients had significantly fewer teeth, higher plaque index and greater attachment loss (Appendix J).

Additional Analyses

Random-effect meta-regressions according to patient characteristics failed to identify any significant modifying effect on periodontitis, number of teeth, and DMFT index (Appendix K). Reporting biases were planned in the initial protocol, but could not be performed due to the limited number of trials included in the meta-analyses.

Sensitivity analysis according to the definition of periodontal disease was conducted by including studies with widely-accepted definition of periodontitis (Appendix L). This indicated that the results of the meta-analyses were robust in all instances. Sensitivity analysis according to the diagnostic criteria used to diagnose IBD, CD, and UC (Appendix M) could not be performed. Further sensitivity analyses were planned, but could not be conducted, due to the number and nature of the included studies

Discussion

Summary of Evidence

In this systematic review, the effect of IBD on periodontal disease and oral health was systematically assessed from eight observational clinical studies of 1 297 patients. According to the results of the meta-analyses, IBD was associated with a significantly increased risk of periodontitis compared to the control group, which was more pronounced in UC rather than in CD.

IBD patients were significantly more likely to have periodontitis, had a higher percentage of sites with increased CAL, and had significantly higher mean PPD (Table 3). The included studies differed at the level of patient oral hygiene or the percentage of patients receiving anti-TNF therapy for IBD [6% (Barros 2007) or 40% (Vavricka et al. 2013)], but this was not reflected into considerable heterogeneity. The association between periodontitis and IBD has been attributed to common predisposing factors, such as age and genetic predisposition, as well as environmental or lifestyle factors (Indriolo et al. 2011). Smoking is strongly associated with both periodontitis (Hujoel et al. 2002) and IBD (Mahid et al. 2006), but has a distinct detrimental role for CD and a protective role for UC (Mahid et al. 2006). Although factors like socio-economic status and smoking, can confound this relationship, and indeed smokers were more heavily affected than non-smokers (Appendix D), adjusted ORs for confounders from included studies were consistent. Some studies have focused on the role of cytokines (McGee et al. 1998, Yucel-Lindberg et al. 1999) or specific pathogenic bacteria on periodontal destruction (Stein et al. 2010) and their alterations in IBD. In fact, it may be more useful to study the mechanisms explaining that the two IBD diseases are associated with periodontitis.

A combination of genetic predisposition, environmental factors and a dysbiotic microbiota with an excessive host response are main etiological factors for the initiation and progression of periodontitis and inflammatory bowel disease (Brandtzaeg 2001, Indriolo et al. 2011). The healthy gut microbiota is mainly composed of strict anaerobes and dominated by Bacteroidetes and Firmicutes. Howerever, in inflammatory bowel disease, the relative abundance of Firmicutes and the diversity of the intestinal microbiota is greatly reduced (Bull & Plummer 2014, Forbes et al. 2016) The oral microbiota is almost as complex as that of the colon and dominated by Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes and Fusobacteria (Wade 2013). During the transition from periodontal health to periodontitis, the microbiota of periodontal pockets shifts from a predominantly Gram-positive aerobic to a predominantly Gram-negative anaerobic dominance (Khan et al. 2015). Periodontitis-associated species include *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Aggregatibacter actinmycetemcomitans,* and many others. However, *Porphyromonas gingivalis*, which has an impressive armamentarium of virulence factors, is

considered a “keystone pathogen”, as this bacterium can cause dysbiosis of the periodontal microbiota, which subsequently results in the destruction of the tooth-supporting tissues (Wade 2013, Khan et al. 2015).

UC patients, both smokers and non-smokers, had worse oral health than CD patients, which suggests that the response to dental plaque may be different between these groups. Indeed, UC and CD differ regarding their immunopathogenesis, which involves the T helper (Th) cell differentiation; CD is considered to be a Th1 disease while UC has characteristics of a Th2 disease (Bouma & Strober 2003). However, a direct explorative comparison (Appendix J) indicated that included UC patients had a significantly higher plaque index than CD patients, which might have confounded this effect.

Although this was not the main scope of this systematic review, the cariological evaluation revealed that IBD had a higher DMFT index (3 studies; table 3; MD=3.85; $p<0.05$), DMF-S index (MD=7.60; $p>0.05$) (Grössner-Schreiber et al. 2006), more dentine caries (OR=2.39; $p<0.05$), higher Decayed index (MD=1.57; $p<0.05$) (Ślebioda et al. 2011), and more oral lesions (OR=7.90; $p<0.05$) than non-IBD patients. This is in accordance with previous reports (Sundh & Hultén 1982, Rooney 1984) and could be attributed to nutrional behavioural changes and alterations in salivary and microbiologic conditions in the oral cavity (Grössner-Schreiber et al. 2006). CD patients have been reported to have an increased intake of refined carbohydrates compared to normal (Schütz et al. 2003) and to prefer sugary to fatty foods, due to its digestability and the concurrently less gastrointestinal symptoms (Järnerot et al. 1983), Additionally, it has been shown that although CD patients have normal saliva flow rate and buffer capacity, the number of salivary mutans streptococci and lactobacilli is higher than normal (Järnerot et al. 1983). The combination of these two findings might explain the increased caries experience of IBD patients, although other studies disagree (Halme et al. 1993, Meurman et al. 1994).

Additionally, intraoral manifestations, including oral lesions, hairy tongue, ulcers, linea alba, and recurrent aphthous stomatitis were more evident both in the composite IBD group, and in the separate CD or UC groups, compared to non-IBD patients (Tables 3; Appendix D, G, and H), which could additionally hamper oral hygiene.

Strengths and Limitations

The strengths of the present review include the pre-defined protocol and outcomes (with deviations from it noted separately in Appendix N), the extensive literature search, and the strict methodology implemented during every stage of it, according to existing evidence-based guidelines. As both university and hospital settings were

included, no specific inclusion criteria were adopted and the included studies were observational of nature, the results could be broadly be generalized to the average patient.

Nevertheless, only a limited number of studies was identified assessing certain outcomes and some of them had uneven samples of IBD and non-IBD patients. Heterogeneity could not be explained in some cases due to the limited number of studies, while publication bias diagnostics and sensitivity analyses could not be performed, which might pose a threat to the results' validity (Papageorgiou 2014b, Papageorgiou et al. 2015c). Additionally, a large number of outcomes reported from included studies were included in the systematic review, but not in the meta-analyses, as only one study contributed to their analysis (Appendix D). It is possible that some significant differences reported by them correspond to actual differences between IBD and non-IBD patients. These can be evaluated in a future update of this review, if additional studies are included. Moreover, although this was not possible to evaluate in this review due to the limited information provided, it would be interesting to know in which cases the diagnosis of perdiodontal disease preceeds IBD or the other way around. Finally, the biggest limitation of this study is that only cross-sectional studies were included, which provide a snapshot picture of the evidence and cannot support a causality between IBD and periodontitis or vice versa.

Conclusion

According to high quality evidence originating from cross-sectional studies, inflammatory bowel disease is significantly associated with increased risk of periodontal disease. Additionally, low quality evidence from cross-sectional studies indicates that patients with inflammatory bowel disease have significantly greater caries experience compared to healthy patients.

Although considerable indications of impaired oral health in inflammatory bowel disease were found from this systematic review, this was based on cross-sectional studies of observational nature, which provide a "snapshot-picture" of a possible underlying pathology. Well-designed prospective controlled longitudinal studies of patients with/without inflammatory bowel disease and periodontitis are direly needed, in order to evaluate the impact of inflammatory bowel disease on oral health and its interrelation with tissue response to periodontic treatment.

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Tables

Table 1. Characteristics of included studies

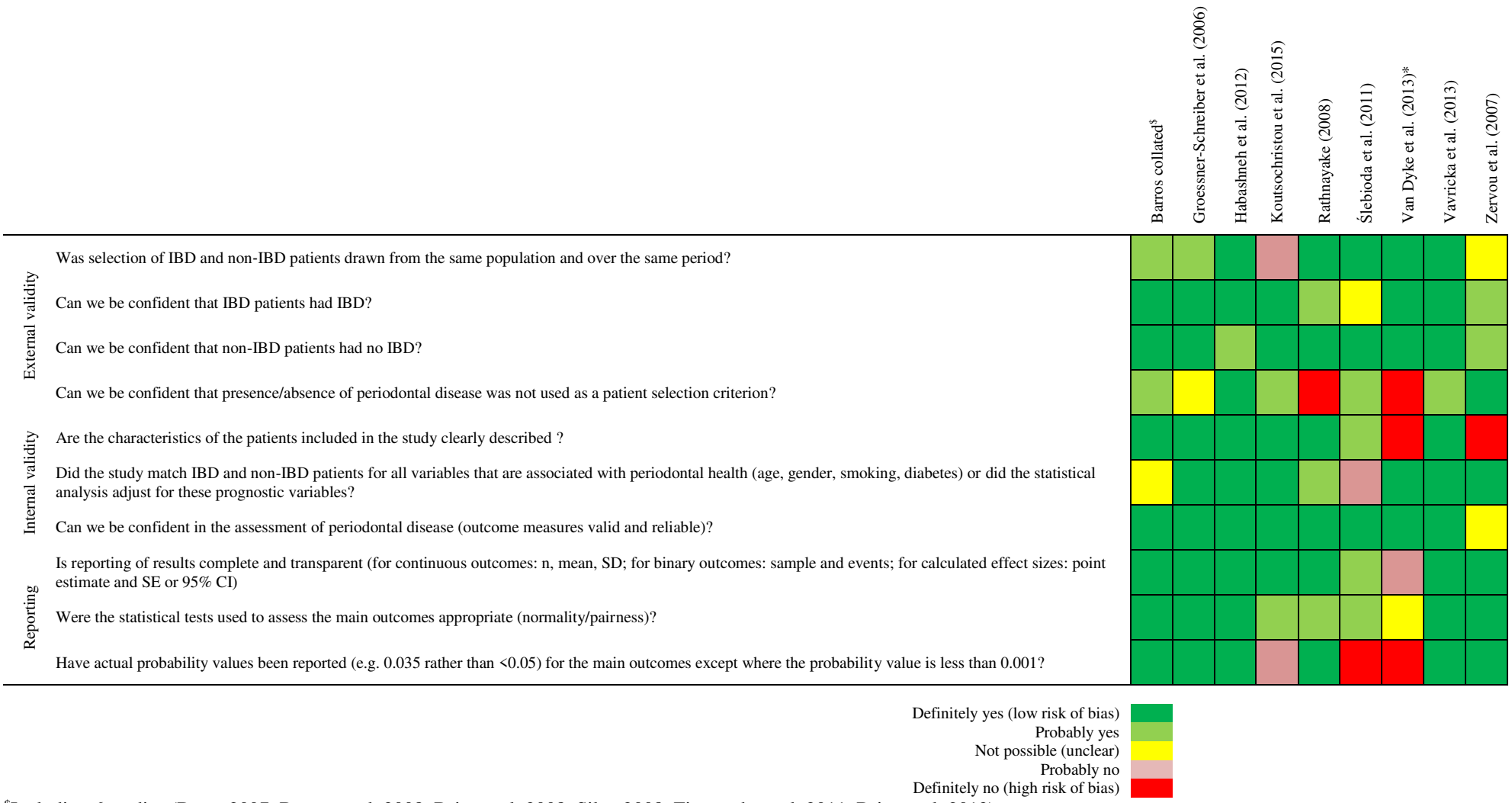
Nr.	Study	Design; setting; language	Patients (no; M/F; mean age)	Extras (ethnicity; smoking; hypertension; diabetes)	IBD	Perio	Oral	Inter
1	Barros collated[$]	CC; University; Brazil; EN/POR	IBD: 179 (64/115) pts; 40.9 yrs Ctr: 74 (24/50) pts; 40.3 yrs	53% Caucasian, 37% mixed, 9% African; 38% smokers; 14% hypertension; 1% diabetes	CD: 99 (31/68) pts; 39.0 yrs; 22% active; extraintestinal 51% UC: 80 (33/47) pts; 43.3 yrs; 24% active; extraintestinal 53%	Periodontitis (at least 4 x CAL≥3mm); %PI; %BOP; PPD; CAL; %CAL≥3mm; IL-18; IL-1β; IL-4; IL-6; IFN-γ; various bacteria	#Teeth; DMFT;	91% of CD pts and 100% of UC pts receiving medication
2	Groessner-Schreiber et al. (2006)	CC; University/private practice; Germany; EN	IBD: 62 (24/38) pts; 38.4 yrs Ctr: 59 (24/35) pts; 38.2 yrs	100% Caucasian; 45% smokers	CD: 46 pts; 39% active UC: 16 pts; 25% active Overall	%PI; %BOP; PPD; %CAL≥4mm; %CAL≥5mm	#teeth; DMFS; dentine caries	All IBD receiving medication
3	Habashneh et al. (2012)	CC; University; Jordan; EN	IBD: 160 (94/66) pts; NR Ctr: 100 (62/38) pts; NR	70% smokers; 11% hypertension	CD: 59 (33/26) pts UC: 101 (61/40) pts	Periodontitis; PI; GI; PPD; CAL; GR; %BOP; %PPD≥3; %PPD≥4; %CAL≥3; %CAL≥4; %CAL≥5	-	-
4	Koutsochristou et al. (2015	CC; University; Greecel EN	IBD: 55 (25/30) pts; 12.3 yrs Ctr: 55 (25/30) pts; 12.2 yrs	0% smokers	CD: 36 (18/18) pts UC: 19 (7/12) pts	Periodontal treatment need (CPITN 2-3); %GI; %PI	DMFT	All IBD receiving medication
5	Rathnayake (2008)	CC; University; Sweden; EN	IBD: 30 (15/15) pts; 41.6 yrs Ctr: 15 (7/8) pts; 42.1 yrs	49% Caucasian, 44% mixed, 7% black; 13% smokers; 13% hypertension; 0.2% diabetes	CD: 15 (8/7) pts; 38.2 yrs UC: 15 (7/8) pts; 45.0 yrs 31% extra-intestinal manifestations; 18% active disease	%PI; %BOP; PPD; CAL; %CAL ≥3mm; %CAL ≥4mm; GCF volume; IL-18; IL-12;	#teeth;	96% receiving medications
6	Ślebioda et al. (2011)	CC; University; Poland; EN/PL	IBD: 95 (53/42) pts; 37.3 yrs Ctr: 70 (24/46) pts; 31.6 yrs	No systematic diseases	CD: 70 (37/33) pts; 37.4 yrs UC: 25 (16/9) pts; 37.2 yrs	Periodontal treatment need (CPITN 2-3)	#teeth; DMFT; OHI	-
7	Van Dyke et al. (2013)*	CC; University; USA; EN	IBD:20 (NR) pts; NR yrs Ctr: 20 (NR) pts; NR yrs	Smoking up to 10 cg/day	(Only for the IBD & PD subgroup) CD: 6 (NR) pts; NR yrs UC 4 (NR) pts; NR yrs	Redness; BOP; CAL; CF-PGE2 levels	-	50% taking steroids
8	Vavricka et al. (2013)	CC; University; Switzerland; EN	IBD: 113 (65/48) pts; 40.6 yrs Ctr: 113 (58/55) pts; 41.7 yrs	58% smokers	CD: 69 (37/32) pts; 39.6 yrs UC: 44 (28/16) pts; 42.3 yrs	PPD; CAL; CAL at deepest pocket; %BOP; %PBI	DMFT	About 73% receiving medication and 36% had surgery
9	Zervou et al. (2007)	CC; state hospital; Greece; EN	IBD: 30 (NR) pts; 40.0 yrs Ctr: 47 (NR) pts; 43.0 yrs	-	CD: 15 pts UC: 15 pts Overall 67% active	Periodontitis; gingivitis; gingival bleeding	-	80% receiving medication

*various non-periodontal outcomes relating to IBD microbiota, neutrophil chemotaxis, phagocytosis, inhibition of neutrophil function were omitted.

[$]Including 6 studies (Barro 2007, Barros et al. 2008, Brito et al. 2008, Silva 2008, Figueredo et al. 2011, Brito et al. 2013).

M/F, male/female; IBD, inflammatory bowel disease; CC, case-control; EN, English; POR, Portuguese; Ctr, control; pts, patients; yrs, years; CD, Crohn's disease; UC, ulcerative colitis; CAL, clinical attachment loss; PI, plaque index; BOP, bleeding on probing; PPD, pocket probing depth; IL, interleukin; IFN, interferon; DMFT, decayed-missing-filled-teeth index; DMFS, decayed-missing-filled-surfaces index; GI, gingival index; GR, gingival recession; GCF, gingival crevicular fluid; PL, Polish; CPITN, community periodontal index of treatment need; OHI, oral health index; NR, not reported; CF-PGE2, prostaglandin E2 in gingival crevicular fluid; PBI, papilla bleeding index.

Table 2. Methodological inadequacies associated with risk of bias within the included studies



[$]Including 6 studies (Barro 2007, Barros et al. 2008, Brito et al. 2008, Silva 2008, Figueredo et al. 2011, Brito et al. 2013).

Table 3. Results of meta-analyses comparing patients with inflammatory bowel disease (combined Crohn's disease and ulcerative colitis) compared to healthy patients

		Effect size			Heterogeneity	
Outcomes	Studies	MD, SMD, or OR (95% CI)	p	95% PrI	I^2 (95% CI)	τ^2
Primary outcome						
Periodontitis	4	OR: 4.55 (3.00,6.91)	<0.001	1.83,11.36	0 (0,68)	0
Secondary outcomes						
Number of teeth	4	MD: -1.00 (-2.15,0.16)	0.090	-5.30,3.31	48 (0,81)	0.656
DMFT index	4†	MD: 3.85 (2.36,5.34)	<0.001	-2.54,10.24	74 (0,89)	1.626
Plaque index	#					
Gingival index	2‡	SMD: 1.19 (0.75,1.63)	<0.001	NA	71 (NA)	0.073
Bleeding on probing	4	MD: 1.90 (-3.21,7.01)	0.466	-19.10,22.91	69 (0,87)	17.033
Clinical attachment loss	[a]					
Clinical attachment loss > 3mm	2	MD: 8.88 (1.48,16.27)	0.019	NA	52 (NA)	15.535
Clinical attachment loss > 4mm	2	MD: 11.52 (1.82,21.23)	0.020	NA	68 (NA)	34.435
Clinical attachment loss > 5mm	2	MD: 3.72 (1.84,5.60)	<0.001	NA	0 (NA)	0
Pocket probing depth	3[b,*]	MD: 0.63 (0.16,1.10)	0.008	-5.37,6.63	97 (94,98)	0.165
Pocket probing depth > 3mm	2	MD: 0.10 (-2.75,2.94)	0.948	NA	0 (NA)	0
Pocket probing depth > 4mm	3[c,*]	MD: -3.45 (-10.46,3.55)	0.334	-88.64,81.74	94 (NA)	32.178
Periodontal treatment need (CPITN 2-3)	2	OR: 6.10 (2.50,14.93)	<0.001	NA	60 (NA)	0.255
Oral lesions	3*	OR: 7.90 (1.46,42.61)	0.016	0, $>10^9$	93 (80,96)	1.756
Angular cheilitis	2	OR: 8.26 (0.53,128.31)	0.131	NA	65 (NA)	2.635
Aphthous lesions	3	OR: 2.45 (1.18,5.12)	0.017	0.00,1 829.56	29 (0,80)	0.130
Hairy tongue	2	OR: 8.01 (0.97,66.33)	0.054	NA	0 (NA)	0
Ulceration	2	OR: 9.10 (1.12,74.28)	0.039	NA	0 (NA)	0

MD, mean difference; OR, odds ratio; CI, confidence interval; PrI, predictive interval; NA, not applicable; DMFT, decayed missing filling teeth; CPITN, Community Periodontal Index of Treatment Needs.

[#]Standardized Mean Difference (SMD) used instead of MD to combine two different plaque indeces (O Leary index and Sillness index); meta-analysis omitted due to heterogeneity: 5 studies highly dispersed on both sides (SMD=0.12; 95% CI=-0.29,0.52; P=0.579; I^2=86%); omission of a single trial not feasible.

*extreme heterogeneity, but agrees on direction; effect magnitude might be imprecise.

†moderate to high heterogeneity, but agrees on direction and the calculated inconsistency (I^2) has large uncertainty interval 0% to 89%; meta-analysis judged as safe .

[a] Meta-analysis omitted; three studies with extreme heterogeneity; studies evenly distributed (MD=0.23; 95% CI=-0.25,0.71; p=0.349; I^2=87).

[b] Omitted study of Groessner-Schreiber et al. (2006) due to homogeneity; results might be unstable (original: MD=0.46; 95% CI=0.04,0.87; p=0.030; I^2=97).

[c] Omitted study of of Groessner-Schreiber et al. (2006) due to homogeneity; results might be unstable (original: MD=-2.20; 95% CI=-7.31,2.91; p=0.399; I^2=90).

Table 4. Summary of findings table with the risk of bias assessment across studies (GRADE approach)

Patients: patients of any age, sex or ethnicity
Settings: university clinics (Brazil, Greece, Jordan, Switzerland) and state hospital (Greece)
Intervention (exposure): inflammatory bowel disease (Crohn's disease and ulcerative colitis)
Comparison: control (no inflammatory bowel disease)

Outcomes	Illustrative comparative risks/changes (95% CI)		Patients (trials)	GRADE	Comments
	IBD-free patients	IBD patients			
	Assumed risk per 1 000 patients (range)	Corresponding risk per 1 000 patients (95% CI)			
Periodontitis					
IBD	468 patients per 1 000 (range 0 to 797)	332 more patients per 1 000 (257 to 388 more) compared to healthy patients.	811 (4)	High[1,2] ⊕⊕⊕⊕	NNT=4 (3 to 4)
CD		309 more patients per 1 000 (211 to 384 more) compared to healthy patients.	572 (4)	High[2,3] ⊕⊕⊕⊕	NNT=4 (3 to 5)
UC		351 more patients per 1 000 (252 to 421 more) compared to healthy patients.	508 (3)	High[1,2] ⊕⊕⊕⊕	NNT=3 (3 to 4)
	Assumed levels (range)	Corresponding levels (95% CI)			
Number of teeth					
IBD	25.14 teeth (range 23.70 to 26.72)	Decrease by 1.00 teeth (2.15 decrease to 0.16 increase) compared to healthy patients.	578 (4)	Low ⊕⊕⊖⊖	
CD		Decrease by 0.11 teeth (1.52 decrease to 1.31 increase) compared to healthy patients.	381 (3)	Low ⊕⊕⊖⊖	
UC		Decrease by 1.86 teeth (0.04 to 3.68 decrease) compared to healthy patients.	337 (3)	Low ⊕⊕⊖⊖	
DMFT index					
IBD	7.70 (range 2.04 to 12.50)	Increase by 3.85 (2.36 to 5.34 increase) compared to healthy patients	749 (4)	Low ⊕⊕⊖⊖	
CD		Increase by 3.73 (0.70 to 6.75 increase) compared to healthy patients	491 (3)	Low ⊕⊕⊖⊖	
UC		Increase by 3.97 (1.94 to 6.00 increase) compared to healthy patients	402 (3)	Low ⊕⊕⊖⊖	

All judgements start from "low", due to the vast inclusion of non-randomized studies.
[1]Rated up by two levels for very large effect included in the confidence and predictive interval.
[2]Rated up by one; estimates adjusted for confounders confirmed results agree with original analyses.
[3]Rated up by one level for large effect included in the confidence and predictive interval.

CI, confidence interval; IBD, inflammatory bowel disease; NNT, number needed to treat; CD, Crohn's disease; UC, ulcerative colitis.

Figure Legends

Fig. 1. Flow diagram that depicts the workflow of identifying qualifying studies.

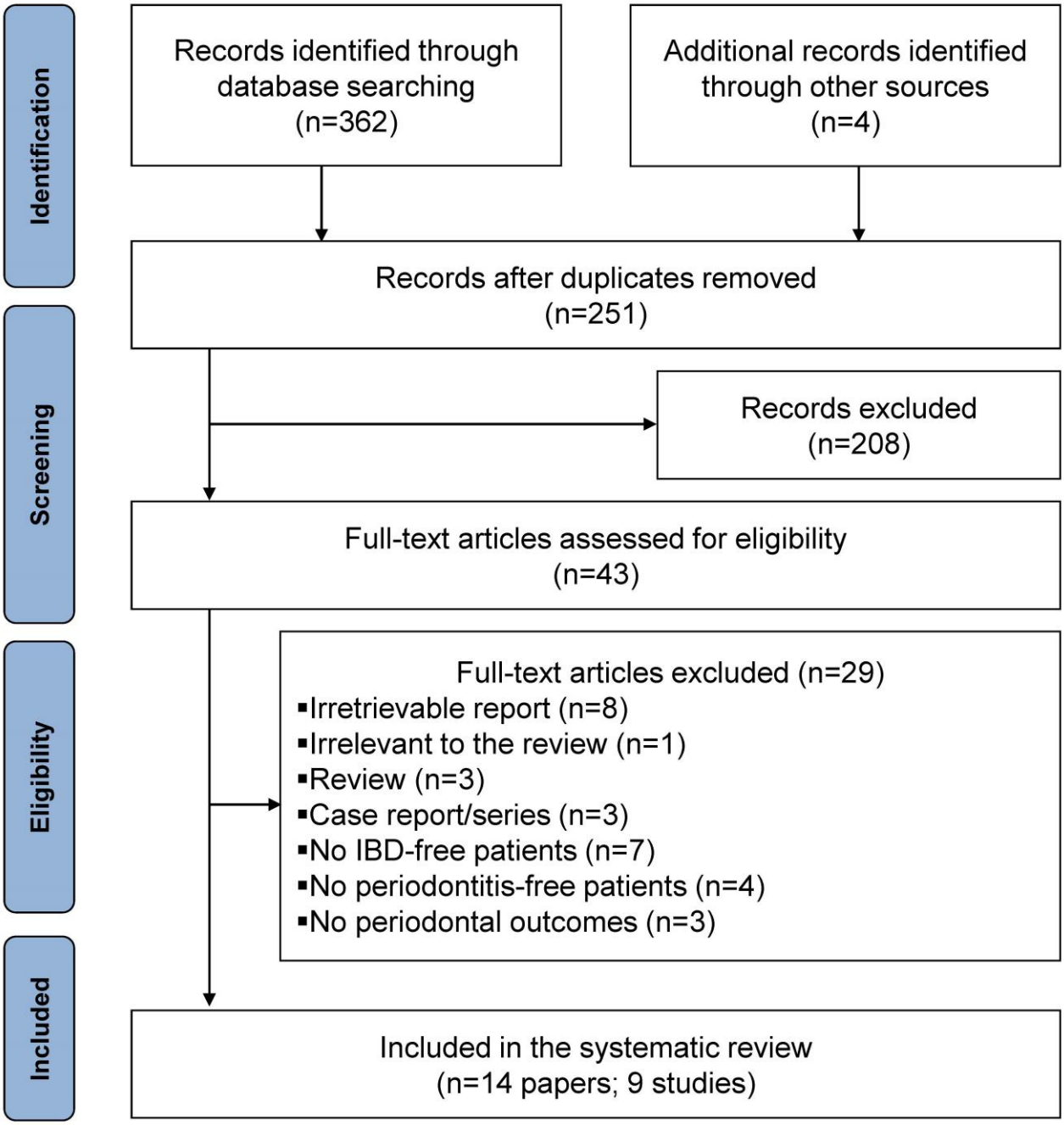
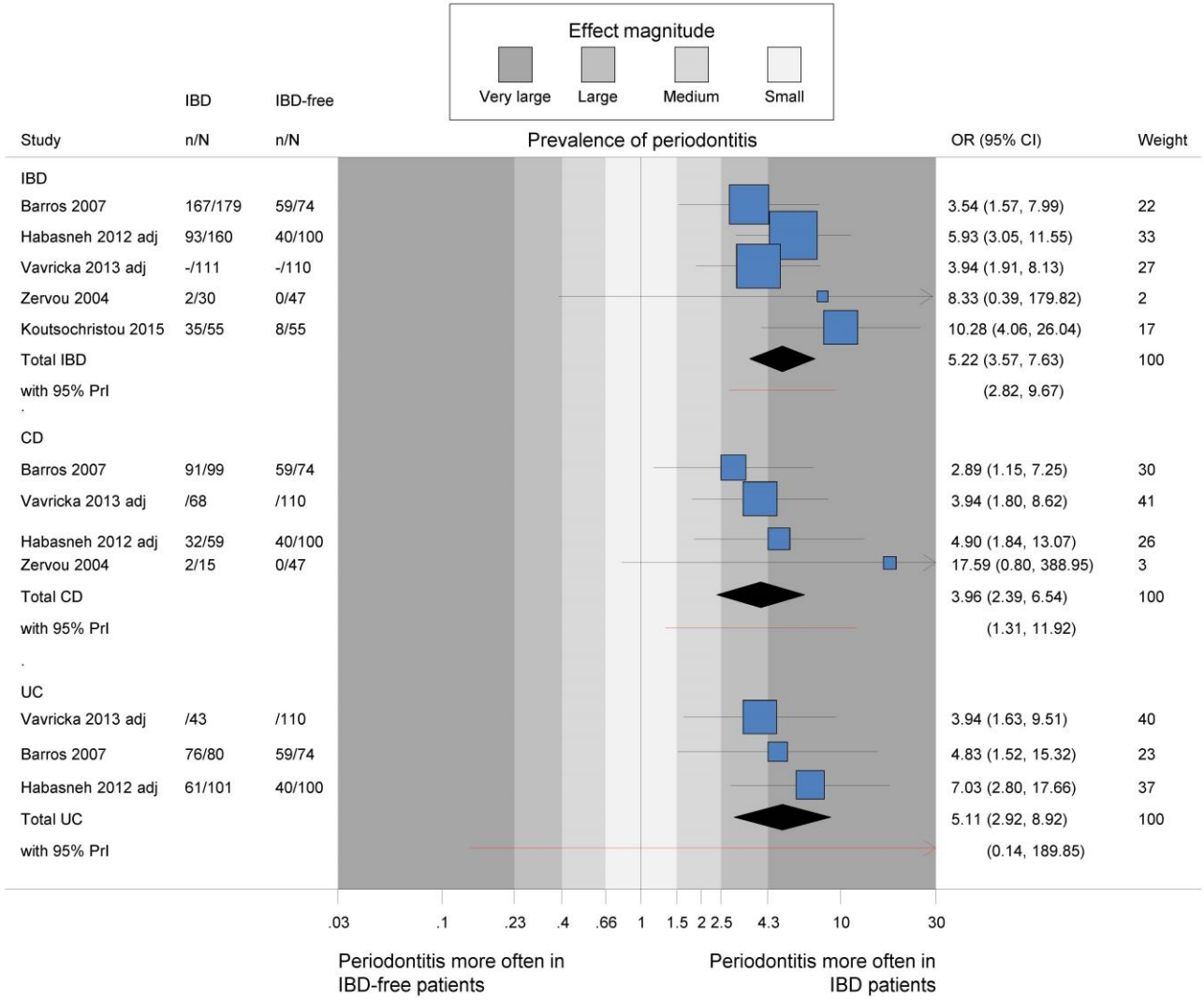


Fig. 2. Forest plot with the meta-analyses regarding the prevalence of periodontitis. IBD, inflammatory bowel disease; n, affected patients; N, sample; OR, odds ratio; CI, confidence interval; adj, adjusted estimates; PrI, predictive interval; CD, Crohn's disease; UC, ulcerative colitis.



Inflammatory bowel disease and oral health: systematic review and a meta-analysis

Supplementary Data

Appendix S1 - Eligibility criteria used in this systematic review according to the PICOS approach.

Characteristic	Inclusion criteria	Exclusion criteria
Observational analysis (prevalence of periodontitis)		
Patients	Patients of any age or sex	-
Intervention (here exposure)	Diagnosis of some type of IBD.	No patients with some type of IBD.
Comparison	Absence of IBD.	No comparison with IBD-free patients.
Outcome	Periodontal health. Primary outcome: periodontitis. Secondary outcomes: any outcome pertaining to (a) clinical periodontal outcome, (b) markers of periodontal inflammation.	Absence of periodontal outcomes.
Study design	Studies of observational nature are eligible for this analysis. If provided, prevalence data will be also included from RCTs. Any clinical setting will be included.	Animal studies and non-clinical studies will be excluded.
Interventional analysis (effect of periodontal or IBD treatment)		
Characteristic	**Inclusion criteria**	**Exclusion criteria**
Patients	Patients of any age or sex with IBD and/or periodontal disease.	-
Intervention	Any kind of intervention addressing the periodontal disease or the IBD.	No intervention addressing the periodontal disease or the IBD.
Comparison	Comparison of patients similar to the intervention/exposure group, but without IBD.	
Outcome	Same types of outcomes as in Table S1a. Eligible outcomes include assessing periodontal disease outcomes before & after treatment for the IBD or IBD disease outcomes before &,after treatment for the periodontal disease	No association of periodontal or IBD treatment with the outcomes of the other disease.
Study design	Both randomized and non-randomized controlled human trials will be included (Papageorgiou et al. 2014). If serious methodological discrepancies between the two study designs are found (Papageorgiou et al., 2015), they will be assessed separately. Any clinical setting will be included.	Animal studies, clinical non-interventional and non-clinical studies will be excluded.

IBD, inflammatory bowel disease; RCT, randomized controlled trial.

Appendix S2. Search strategies used for each database with the corresponding results (last search Jan 2017).

Electronic database	Search strategy used	Limits	Hits up to May 2015	Update up to Jan 2017
General sources				
CDSR searched via Cochrane Library www.thecochranelibrary.com	periodon* AND ("inflammatory bowel" OR "ulcerative colitis" OR "Crohn's disease" OR "Crohn disease")	All text	1	1
CENTRAL searched via Cochrane Library www.thecochranelibrary.com				
DARE searched via Cochrane Library www.thecochranelibrary.com				
MEDLINE (MeSH Terms) searched via PubMed www.ncbi.nlm.nih.gov/sites/entrez/	periodon* AND ("inflammatory bowel" OR "ulcerative colitis" OR "Crohn's disease" OR "Crohn disease")	Limit to humans	91	16
Scopus www.scopus.com	periodon* AND ("inflammatory bowel" OR "ulcerative colitis" OR "Crohn's disease" OR "Crohn disease")	Title/abstract/keywords Limit to dentistry	44	6
Open access sources				
DOAJ http://www.doaj.org/	-"inflammatory bowel disease" AND periodon* -Crohn AND periodon* -"ulcerative colitis" AND periodon*	All fields	6	0
Regional sources				
VHL http://regional.bvsalud.org/php/index.php?lang=en	periodon* AND ("inflammatory bowel" OR "ulcerative colitis" OR Crohn)	Exclude MEDLINE and CENTRAL	16	1
Scielo http://www.scielo.org/php/index.php?lang=en	("inflammatory bowel" OR Crohn OR "ulcerative colitis") AND periodon*	-	0	0
Grey literature sources				
Digital Dissertations searched via UMI/ProQuest http://proquest.umi.com/login	periodon* AND ("inflammatory bowel" OR "ulcerative colitis" OR "Crohn's disease" OR "Crohn disease")	Limit to Dentistry	54	8
German National Library of Medicine (ZB MED) http://www.medpilot.de	("inflammatory bowel" OR Crohn OR "ulcerative colitis") AND periodon*	Limit to Medizin/Gesundheit Exclude MEDLINE, Books	5	0
ISI Web of Knowledge http://apps.webofknowledge.com/	periodon* AND ("inflammatory bowel" OR "ulcerative colitis" OR "Crohn's disease" OR "Crohn disease")	Topic Limit to Dentristry oral surgery medicine	112	0
WHO trial search portal http://apps.who.int/trialsearch/	("inflammatory bowel" OR Crohn OR "ulcerative colitis") AND periodon*	-	0	0
OpenSIGLE http://www.opengrey.eu/	("inflammatory bowel" OR Crohn OR "ulcerative colitis") AND periodon*	-	1	0
Overall articles from electronic search			330	32

$ Highly-sensitive search strategy tested, in all databases, but included too few results and was omitted in many databases.

BBO, Bibliografia Brasileira de Odontologia; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; DOAJ, Database of Open Access Journals; ISI, Institute for Scientific Information; LILACS, Literatura Latino-Americana e do Caribe em Ciências da Saúde; MeSH, Medical Subject Headings; Scielo, Scientific Eletronic Library on line; UMI, University Microfilms International; WHO, World Health Organization.

Appendix S3. List of excluded/included studies.

Nr.	Paper	
1	Acharya AAMDPSTKY. Developing an electronic dental record information model for general dentistry [3416882]: University of Medicine and Dentistry of New Jersey; 2010.	Excluded by title
2	Alasqah MAZDY. Salivary Biomarkers of Periodontal Disease in Smoker and Non-Smoker Periodontitis Patients [1555895]: Tufts University School of Dental Medicine; 2014.	Excluded by title
3	Albilia JATHY. Serum BMP-2, 4, 7 and AHSG in Patients with Heterotopic Ossification Following Arthroplasty [Mr82350]: University of Toronto (Canada); 2011.	Excluded by title
4	Bhatt AALAY. Mesenchymal stem cells from human gingiva ameliorate murine alimentary mucositis [1496953]: University of Southern California; 2011.	Excluded by title
5	Calhoun CCACRY. Cellular functions of cyclophilin A in actin stability and cyclosporine A induced-gingival overgrowth [3356521]: University of California, Los Angeles; 2008.	Excluded by title
6	Champaiboon CAHMCY. Calprotectin S100A9 structural domains regulate epithelial cell resistance to bacterial invasion [3338934]: University of Minnesota; 2008.	Excluded by title
7	Chino TACEAY. Regulation of inflammation and homeostatsis of oral mucosal tissue by dendritic cells [3345634]: University of Washington; 2008.	Excluded by title
8	Chou C-HADSRSMY. Association of Selected Candidate Gene Polymorphisms with Periodontal Disease [3483535]: University of Medicine and Dentistry of New Jersey; 2011.	Excluded by title
9	Divaris KAOAFY. Exploring the genetic basis of chronic periodontitis: A genome-wide approach [3495471]: The University of North Carolina at Chapel Hill; 2011.	Excluded by title
10	El-Awady AACCY. Porphyromonas gingivalis Escape-from Autophagy in Human Myeloid Dendritic Cells via Minor Mfa-1 Fimbra-DC-Sign Interactions [3579936]: Georgia Regents University; 2014.	Excluded by title
11	Eskan MAY. Age-associated changes in innate immunity and their impacts on inflammatory disease [3502286]: University of Louisville; 2011.	Excluded by title
12	Fiedler LY. Role of decorin in control of endothelial cell behaviour [U584185]: Cardiff University (United Kingdom); 2007.	Excluded by title
13	Fleming PPABPHY. The effects of 2-DeNT oral topical powder on minor recurrent aphthous ulcers [1539091]: The Texas A&M University System Health Science Center; 2013.	Excluded by title
14	Fredman GBAVDTEY. Resolvin E1 regulation of platelet functions: Novel pathways in resolution [3357646]: Boston University; 2009.	Excluded by title
15	Freire MAZHHY. Antibody mediated osseous regeneration [3513760]: University of Southern California; 2012.	Excluded by title
16	George JASDY. Cigarette smoke promotes genomic evolution in the periodontal pathogen Porphyromonas gingivalis [1527649]: University of Louisville; 2013.	Excluded by title
17	Ghadiri JAAOCCY. The prevalence of the uncultivated bacterium TM7a in human subgingival plaque [1547092]: San Jose State University; 2013.	Excluded by title
18	Hitimana HY. The Association between Functional Foods and Dental Caries Experience [Mr67042]: McGill University (Canada); 2009.	Excluded by title
19	Horst OVAD-CBAY. Defense mechanisms in human tooth pulp: Odontoblast functions [3328407]: University of Washington; 2008.	Excluded by title
20	Jaffray ECY. Characterisation of paediatric odontogenic bacteraemia [U591972]: University of London, University College London (United Kingdom); 2006.	Excluded by title
21	Lenga YY. Osteopontin expression is required for myofibroblast differentiation [Mr44972]: University of Toronto (Canada); 2008.	Excluded by title
22	Loner CMY. Click scaffolds for the inhibition of Porphyromonas gingivalis and Streptococcus gordonii biofilm formation [1521240]: University of Louisville; 2012.	Excluded by title
23	Ma WAFSJY. Carbohydrate receptors, preterm labor, and periodontitis [3412216]: University of California, San Francisco; 2010.	Excluded by title
24	Maria OY. Identification and characterization of a cell source to regenerate salivary glands [Nr72686]: McGill University (Canada); 2010.	Excluded by title
25	McLean-Plunkett EAAMAEY. Vitamin D and Calcium Intake and the Prevalence of Periodontal Disease in Postmenopausal Women [1519937]: State University of New York at Buffalo; 2012.	Excluded by title
26	Nibali LY. Analysis of genetic polymorphisms as risk factors for Aggressive Periodontitis [U592181]: University of London, University College London (United Kingdom); 2006.	Excluded by title
27	Noueihed CY. An investigation of the effect of neighbourhood characteristics on traumatic	Excluded by title

	dental injuries among a sample of Quebec children [Mr56862]: McGill University (Canada); 2009.	
28	Odusanwo OAABOJY. Resolvin D1 prevents TNF-alpha-mediated disruption of salivary epithelial formation [1500493]: State University of New York at Buffalo; 2011.	Excluded by title
29	Oluwadara OOACFY. Molecular Biomarker Profiling and Translational Evidence-Based Dentistry in Oral Lichen Planus and Oral Squamous Cell Carcinoma [3446847]: University of California, Los Angeles; 2010.	Excluded by title
30	Paes Batista da Silva AAOSY. Bacterial Characterization in Health and Periodontal Diseases During Induced Gingival Inflammation [1513063]: The University of North Carolina at Chapel Hill; 2012.	Excluded by title
31	Paes Batista da Silva AY. Role of Osteopontin During Dextran Sulfate Sodium-induced Colitis [Nr67676]: University of Toronto (Canada); 2009.	Excluded by title
32	Papathanasiou EAGTTTCY. Levels of interferon-gamma (IFN-gamma), interleukin-4 (IL-4), interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP) in gingival crevicular fluid from patients with chronic periodontitis [1514563]: Tufts University School of Dental Medicine; 2012.	Excluded by title
33	Park MSMY. Oral health status in children undergoing treatment for neutropenia [Mr76204]: University of Toronto (Canada); 2011.	Excluded by title
34	Patil CSAKKLY. Targeting mRNA stability as a potential therapeutic for LPS-induced inflammatory bone loss [3344637]: State University of New York at Buffalo; 2007.	Excluded by title
35	Phattarataratip EABJAY. The role of salivary antimicrobial peptides in shaping Streptococcus mutans ecology [3422183]: The University of Iowa; 2010.	Excluded by title
36	Phillips CRAKKBY. A qualitative survey of orthodontic extraction related patient information available on the World Wide Web [1585315]: Saint Louis University; 2014.	Excluded by title
37	Pongpichit BY. The prevalence and extent of school absences and factors related to absences caused by dental conditions and dental care in Thai schoolchildren [U593118]: University of London, University College London (United Kingdom); 2006.	Excluded by title
38	Prakasam SACCY. Modulating immune responses of Langerhans cells against microbial associated molecular patterns [3401725]: State University of New York at Stony Brook; 2009.	Excluded by title
39	Sahli MWAMAEY. The association between plasma 25-hydroxyvitamin D concentration and oral bacteria among postmenopausal women [1519952]: State University of New York at Buffalo; 2012.	Excluded by title
40	Scheller ELAKPHY. Regulation of bone formation and pathology by local actions of leptin in the bone marrow [3493053]: University of Michigan; 2011.	Excluded by title
41	Schwarzberg KAKSTY. Oral polymicrobial communities and impact on human health [3609026]: San Diego State University; 2013.	Excluded by title
42	Sculley DVY. Inter-individual variation in saliva antioxidant status in relation to periodontal disease [U191563]: University of Leicester (United Kingdom); 2004.	Excluded by title
43	Seif MMAJS-JY. Etiopathology of autoimmune disease and dental perspectives [1559614]: Boston University; 2014.	Excluded by title
44	Seville LY. Study of tetracycline resistance determinants and their genetic supports in the oral and faecal metagenomes of six European countries [U592369]: University of London, University College London (United Kingdom); 2007.	Excluded by title
45	Shapiro JLAPMLY. The endocytosis of enamel matrix protein derivatives [3368646]: University of Southern California; 2009.	Excluded by title
46	Shrestha DAYPY. Implementing Teledentistry in Nepal: Using Mobile Phone and Internet as Store-and-Forward Method [1507181]: University of California, Davis; 2011.	Excluded by title
47	Singer JAAJSY. Vitamin D and chronic pain: A comprehensive review [1545731]: Temple University; 2013.	Excluded by title
48	Villoria PAHVY. A clinical study to assess effect of oral hygiene with a probiotic organism on dental plaque pH and on plaque bacteria including Streptococcus mutans [1546977]: State University of New York at Buffalo; 2013.	Excluded by title
49	Yezdani GAZPY. Role of VDR in host immune response to Porphyromonas gingivalis infection [1499774]: The University of Alabama at Birmingham; 2011.	Excluded by title
50	Zhang GARJDY. Streptococcus cristatus modulates epithelial innate immune response through regulating nuclear factor-kappa B pathway [3389387]: University of Minnesota; 2009.	Excluded by title
51	Zhang SAOSY. Regulation of Inflammatory Genes Involved in Periodontal Diseases by	Excluded by title

	DNA Methylation [3464948]: The University of North Carolina at Chapel Hill; 2011.	
52	Zhang SAOSY. Expression of interleukin-37 (IL37) and the genetic variations of IL37 in relation to chronic periodontitis [1557234]: The University of North Carolina at Chapel Hill; 2014.	Excluded by title
53	Abo T, Kawamura T, Kawamura H, Tomiyama-Miyaji C, Kanda Y. Relationship between diseases accompanied by tissue destruction and granulocytes with surface adrenergic receptors. Immunologic research. 2007;37(3):201-10. Epub 2007/09/18.	Excluded by title
54	Ayangco L, Rogers RS, 3rd, Sheridan PJ. Pyostomatitis vegetans as an early sign of reactivation of Crohn's disease: a case report. J Periodontol. 2002;73(12):1512-6. Epub 2003/01/28.	Excluded by title
55	Barksby HE, Lea SR, Preshaw PM, Taylor JJ. The expanding family of interleukin-1 cytokines and their role in destructive inflammatory disorders. Clinical and experimental immunology. 2007;149(2):217-25.	Excluded by title
56	Castellanos JL. [Periodontal immunopathology]. Revista ADM : organo oficial de la Asociacion Dental Mexicana. 1985;42(5):149-54. Epub 1985/09/01. Immunopatologia parodontal.	Excluded by title
57	Chi AC, Neville BW, Krayer JW, Gonsalves WC. Oral manifestations of systemic disease. American family physician. 2010;82(11):1381-8.	Excluded by title
58	Diegelmann J, Czamara D, Le Bras E, Zimmermann E, Olszak T, Bedynek A, et al. Intestinal DMBT1 expression is modulated by Crohn's disease-associated IL23R variants and by a DMBT1 variant which influences binding of the transcription factors CREB1 and ATF-2. PloS one. 2013;8(11):e77773.	Excluded by title
59	Duran-Pinedo AE, Paster B, Teles R, Frias-Lopez J. Correlation network analysis applied to complex biofilm communities. PloS one. 2011;6(12):e28438. Epub 2011/12/14.	Excluded by title
60	Elias MK, Mateen FJ, Weiler CR. The Melkersson-Rosenthal syndrome: a retrospective study of biopsied cases. Journal of neurology. 2013;260(1):138-43. Epub 2012/07/28.	Excluded by title
61	Folwaczny M, Glas J, Torok HP, Limbersky O, Folwaczny C. Toll-like receptor (TLR) 2 and 4 mutations in periodontal disease. Clinical and experimental immunology. 2004;135(2):330-5. Epub 2004/01/24.	Excluded by title
62	Fry L, Baker BS, Powles AV, Fahlen A, Engstrand L. Is chronic plaque psoriasis triggered by microbiota in the skin? The British journal of dermatology. 2013;169(1):47-52. Epub 2013/03/26.	Excluded by title
63	Garrido-Mesa N, Zarzuelo A, Galvez J. Minocycline: far beyond an antibiotic. British journal of pharmacology. 2013;169(2):337-52. Epub 2013/02/28.	Excluded by title
64	Glade MJ. Vitamin D: health panacea or false prophet? Nutrition (Burbank, Los Angeles County, Calif). 2013;29(1):37-41. Epub 2012/10/23.	Excluded by title
65	Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nature reviews Microbiology. 2012;10(10):717-25. Epub 2012/09/04.	Excluded by title
66	Healy CM, Farthing PM, Williams DM, Thornhill MH. Pyostomatitis vegetans and associated systemic disease. A review and two case reports. Oral surgery, oral medicine, and oral pathology. 1994;78(3):323-8.	Excluded by title
67	Hofstad T. Immune responses to anaerobic gram-negative bacteria in health and disease. Die Nahrung. 1984;28(6-7):717-21. Epub 1984/01/01.	Excluded by title
68	Ichiishi S, Tanaka K, Nakao K, Izumi K, Mikamo H, Watanabe K. First isolation of Desulfovibrio from the human vaginal flora. Anaerobe. 2010;16(3):229-33. Epub 2010/02/18.	Excluded by title
69	Ingram C. Melkersson-Rosenthal syndrome or oro-facial granulomatosis (OFG): an update. Journal of the New Zealand Society of Periodontology. 1999(84):24-5. Epub 2000/05/24.	Excluded by title
70	Jorth P, Turner KH, Gumus P, Nizam N, Buduneli N, Whiteley M. Metatranscriptomics of the human oral microbiome during health and disease. mBio. 2014;5(2):e01012-14. Epub 2014/04/03.	Excluded by title
71	Kaakoush NO, Mitchell HM. Campylobacter concisus - A new player in intestinal disease. Frontiers in cellular and infection microbiology. 2012;2:4. Epub 2012/08/25.	Excluded by title
72	Kuehbacher T, Rehman A, Lepage P, Hellmig S, Folsch UR, Schreiber S, et al. Intestinal TM7 bacterial phylogenies in active inflammatory bowel disease. Journal of medical microbiology. 2008;57(Pt 12):1569-76.	Excluded by title
73	Kverka M, Tlaskalova-Hogenova H. Two faces of microbiota in inflammatory and autoimmune diseases: triggers and drugs. APMIS : acta pathologica, microbiologica, et	Excluded by title

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74	Ladero JM. Influence of polymorphic N-acetyltransferases on non-malignant spontaneous disorders and on response to drugs. Current drug metabolism. 2008;9(6):532-7. Epub 2008/08/06.	Excluded by title
75	Lakschevitz FS, Glogauer M. High-purity neutrophil isolation from human peripheral blood and saliva for transcriptome analysis. Methods in molecular biology (Clifton, NJ). 2014;1124:469-83. Epub 2014/02/08.	Excluded by title
76	Lazaro P. [Oral rehabilitation of a patient with Crohn's disease]. Le Chirurgien-dentiste de France. 1990;60(544-545):57-64. Epub 1990/12/20. Rehabilitation buccale chez un sujet atteint de maladie de Crohn.	Excluded by title
77	Lodowska J, Wolny D, Jaworska-Kik M, Kurkiewicz S, Dzierzewicz Z, Weglarz L. The chemical composition of endotoxin isolated from intestinal strain of Desulfovibrio desulfuricans. TheScientificWorldJournal. 2012;2012:647352. Epub 2012/05/26.	Excluded by title
78	Loos BG, Fiebig A, Nothnagel M, Jepsen S, Groessner-Schreiber B, Franke A, et al. NOD1 gene polymorphisms in relation to aggressive periodontitis. Innate immunity. 2009;15(4):225-32. Epub 2009/07/10.	Excluded by title
79	Nibali L, Donos N, Henderson B. Periodontal infectogenomics. Journal of medical microbiology. 2009;58(Pt 10):1269-74. Epub 2009/06/17.	Excluded by title
80	Ogawa T, Tarkowski A, McGhee ML, Moldoveanu Z, Mestecky J, Hirsch HZ, et al. Analysis of human IgG and IgA subclass antibody-secreting cells from localized chronic inflammatory tissue. Journal of immunology (Baltimore, Md : 1950). 1989;142(4):1150-8. Epub 1989/02/15.	Excluded by title
81	Pagoldh M, Lange S, Jennische E, Almer S, Bostrom EA, Eriksson A. Faecal analysis and plasma complement factor 3c levels at admission for an acute attack of ulcerative colitis are predictive of the need for colectomy. European journal of gastroenterology & hepatology. 2014;26(3):295-300. Epub 2014/01/15.	Excluded by title
82	Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. Nature reviews Drug discovery. 2012;11(3):234-50. Epub 2012/03/02.	Excluded by title
83	Rees TD. Orofacial granulomatosis and related conditions. Periodontol 2000. 1999;21:145-57. Epub 1999/11/07.	Excluded by title
84	Reismann P, Racz K, Tulassay Z. [Polymorphisms of the Toll-like receptor 4 gene and their potential role in infectious diseases and chronic inflammatory disorders]. Orvosi hetilap. 2008;149(38):1791-9. Epub 2008/09/23. A Toll-like receptor-4-genpolimorfizmusok, valamint lehetseges klinikai szerepuk fertozesekben es kronikus gyulladasos betegsegekben.	Excluded by title
85	Rezaie A, Ghorbani F, Eshghtork A, Zamani MJ, Dehghan G, Taghavi B, et al. Alterations in salivary antioxidants, nitric oxide, and transforming growth factor-beta 1 in relation to disease activity in Crohn's disease patients. Annals of the New York Academy of Sciences. 2006;1091:110-22. Epub 2007/03/08.	Excluded by title
86	Rogers RS, 3rd, Movius DL, Pierre RV. Lymphocyte-epithelial cell interactions in oral mucosal inflammatory diseases. The Journal of investigative dermatology. 1976;67(5):599-602. Epub 1976/11/01.	Excluded by title
87	Sadler E, Klausegger A, Muss W, Deinsberger U, Pohla-Gubo G, Laimer M, et al. Novel KIND1 gene mutation in Kindler syndrome with severe gastrointestinal tract involvement. Archives of dermatology. 2006;142(12):1619-24. Epub 2006/12/21.	Excluded by title
88	Sanz M, van Winkelhoff AJ. Periodontal infections: understanding the complexity--consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol. 2011;38 Suppl 11:3-6. Epub 2011/03/01.	Excluded by title
89	Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Molecular nutrition & food research. 2011;55(1):96-108.	Excluded by title
90	Scott DA, Martin M. Exploitation of the nicotinic anti-inflammatory pathway for the treatment of epithelial inflammatory diseases. World journal of gastroenterology : WJG. 2006;12(46):7451-9. Epub 2006/12/15.	Excluded by title
91	Singh VP, Sharma J, Babu S, Rizwanulla, Singla A. Role of probiotics in health and disease: a review. JPMA The Journal of the Pakistan Medical Association. 2013;63(2):253-7. Epub 2013/07/31.	Excluded by title
92	Steiner M, Ramp WK. Endosseous dental implants and the glucocorticoid-dependent patient. The Journal of oral implantology. 1990;16(3):211-7. Epub 1990/01/01.	Excluded by title

93	Taichman NS, Wilton JM. Leukotoxicity of an extract from Actinobacillus actinomycetemcomitans for human gingival polymorphonuclear leukocytes. Inflammation. 1981;5(1):1-12. Epub 1981/03/01.	Excluded by title
94	Tiedemann C, Wetzel A. [Periodontitis as manifestation of a systemic disease. A case report]. Schweizer Monatsschrift fur Zahnmedizin = Revue mensuelle suisse d'odonto-stomatologie = Rivista mensile svizzera di odontologia e stomatologia / SSO. 2001;111(9):1091-102. Epub 2001/10/26. Parodontitis als Manifestation einer Systemerkrankung. Eine Fallprasentation.	Excluded by title
95	Tlaskalova-Hogenova H, Stepankova R, Hudcovic T, Tuckova L, Cukrowska B, Lodinova-Zadnikova R, et al. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immunology letters. 2004;93(2-3):97-108. Epub 2004/05/26.	Excluded by title
96	van der Bijl P, Broeksma J. Acute bronchospasm following administration of lidocaine. Anesthesia & pain control in dentistry. 1993;2(4):203-5. Epub 1993/01/01.	Excluded by title
97	Wei B, Dalwadi H, Gordon LK, Landers C, Bruckner D, Targan SR, et al. Molecular cloning of a Bacteroides caccae TonB-linked outer membrane protein identified by an inflammatory bowel disease marker antibody. Infection and immunity. 2001;69(10):6044-54. Epub 2001/09/13.	Excluded by title
98	Yeoh N, Burton JP, Suppiah P, Reid G, Stebbings S. The role of the microbiome in rheumatic diseases. Current rheumatology reports. 2013;15(3):314. Epub 2013/02/05.	Excluded by title
99	Aarthi JJ, Darendeliler MA, Pushparaj PN. Dissecting the role of the S1P/S1PR axis in health and disease. Journal of Dental Research. 2011;90(7):841-54.	Excluded by title
100	Alsaadi G, Quirynen M, Komárek A, Van Steenberghe D. Impact of local and systemic factors on the incidence of oral implant failures, up to abutment connection. Journal of Clinical Periodontology. 2007;34(7):610-7.	Excluded by title
101	Alsaadi G, Quirynen M, Komárek A, Van Steenberghe D. Impact of local and systemic factors on the incidence of late oral implant loss. Clinical Oral Implants Research. 2008;19(7):670-6.	Excluded by title
102	Alsaadi G, Quirynen M, Michiles K, Teughels W, Komárek A, Van Steenberghe D. Impact of local and systemic factors on the incidence of failures up to abutment connection with modified surface oral implants. Journal of Clinical Periodontology. 2008;35(1):51-7.	Excluded by title
103	Balshi TJ, Wolfinger GJ. Management of the posterior maxilla in the compromised patient: Historical, current, and future perspectives. Periodontology 2000. 2003;33:67-81.	Excluded by title
104	Dawson DR, Branch-Mays G, Gonzalez OA, Ebersole JL. Dietary modulation of the inflammatory cascade. Periodontology 2000. 2014;64(1):161-97.	Excluded by title
105	Folwaczny M, Glas J, Török HP, Mauermann D, Folwaczny C. The 3020insC mutation of the NOD2/CARD15 gene in patients with periodontal disease. European Journal of Oral Sciences. 2004;112(4):316-9.	Excluded by title
106	Johannsen A, Susin C, Gustafsson A. Smoking and inflammation: Evidence for a synergistic role in chronic disease. Periodontology 2000. 2014;64(1):111-26.	Excluded by title
107	Kebschull M, Demmer R, Behle JH, Pollreisz A, Heidemann J, Belusko PB, et al. Granulocyte chemotactic protein 2 (gcp-2/cxcl6) complements interleukin-8 in periodontal disease. Journal of Periodontal Research. 2009;44(4):465-71.	Excluded by title
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109	Li Z, Jiang CM, An S, Cheng Q, Huang YF, Wang YT, et al. Immunomodulatory properties of dental tissue-derived mesenchymal stem cells. Oral Diseases. 2014;20(1):25-34.	Excluded by title
110	Nagpal S, Acharya AB, Thakur SL. Periodontal disease and anemias associated with Crohn's disease. A case report. The New York state dental journal. 2012;78(2):47-50.	Excluded by title
111	Noack B, Görgens H, Hoffmann T, Schackert HK. CARD15 gene variants in aggressive periodontitis. Journal of Clinical Periodontology. 2006;33(11):779-83.	Excluded by title
112	Ouhara K, Kawai T, Silva MJ, Fujita T, Hayashida K, Karimbux NY, et al. Expression levels of novel cytokine IL-32 in periodontitis and its role in the suppression of IL-8 production by human gingival fibroblasts stimulated with porphyromonas gingivalis. Journal of Oral Microbiology. 2012;4(2012).	Excluded by title
113	Oz HS, Ebersole JL. A novel murine model for chronic inflammatory alveolar bone loss. Journal of Periodontal Research. 2010;45(1):94-9.	Excluded by title
114	Palma-Carrió C, Maestre-Ferrín L, Peñarrocha-Oltra D, Peñarrocha-Diago MA, Peñarrocha-Diago M. Risk factors associated with early failure of dental implants. A	Excluded by title

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116	Pietropaoli D, Del Pinto R, Corridoni D, Rodriguez-Palacios A, Di Stefano G, Monaco A, et al. Occurrence of spontaneous periodontal disease in the SAMP1/YitFc murine model of crohn disease. Journal of Periodontology. 2014;85(12):1799-805.	Excluded by title
117	Schaefer AS, Jochens A, Dommisch H, Graetz C, Jockel-Schneider Y, Harks I, et al. A large candidate-gene association study suggests genetic variants at IRF5 and PRDM1 to be associated with aggressive periodontitis. Journal of Clinical Periodontology. 2014;41(12):1122-31.	Excluded by title
118	Sigusch BW. Periodontitis as manifestation of Crohn's disease in primary dentition: A case report. Journal of Dentistry for Children. 2004;71(3):193-6.	Excluded by title
119	Van Steenberghe D, Jacobs R, Desnyder M, Maffei G, Quirynen M. The relative impact of local and endogenous patient-related factors on implant failure up to the abutment stage. Clinical Oral Implants Research. 2002;13(6):617-22.	Excluded by title
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122	Al-Rasheed A, Scheerens H, Srivastava AK, Rennick DM, Tatakis DN. Accelerated alveolar bone loss in mice lacking interleukin-10: late onset. Journal of Periodontal Research. 2004;39(3):194-8.	Excluded by title
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125	Cotti E, Schirru E, Acquas E, Usai P. An Overview on Biologic Medications and Their Possible Role in Apical Periodontitis. Journal of Endodontics. 2014;40(12):1902-11.	Excluded by title
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Appendix S4 Results of the individual outcomes from the included studies that were not included in meta-analyses.

		IBD vs control		CD vs control		UC vs control	
Outcome	**Study**	**MD (95% CI)**	**P**	**MD (95% CI)**	**P**	**MD (95% CI)**	**P**
SG shallow pockets: IL-4	Barros 2007	-0.85 (-1.71,0.01)	0.052	-0.50 (-1.47,0.47)	0.312	-1.20 (-2.04,-0.36)	**0.005**
Serum IFN-γ	Barros 2007	0.00 (-0.16,0.16)	1.000	0.00 (-0.17,0.17)	1.000	0.00 (-0.15,0.15)	1.000
Serum IL-10	Barros 2007	-1.80 (-11.37,7.77)	0.712	-3.40 (-11.32,4.52)	0.400	-0.30 (-13.55,12.95)	0.965
Serum IL-12p70	Barros 2007	0.00 (-1.24,1.24)	1.000	0.00 (-1.24,1.24)	1.000	0.00 (-1.24,1.24)	1.000
Serum IL-18	Barros 2007	50.71 (10.26,91.16)	**0.014**	48.90 (-4.31,102.11)	0.072	52.40 (3.77,101.03)	**0.035**
Serum IL-4	Barros 2007	0.00 (-4.56,4.56)	1.000	0.00 (-4.44,4.44)	1.000	0.00 (-5.65,5.65)	1.000
Serum IL-6	Barros 2007	0.71 (-7.12,8.54)	0.859	0.40 (-7.60,8.40)	0.922	1.00 (-6.90,8.90)	0.804
SG deep pockets: %PI	Barros 2007	-5.45 (-29.21,18.31)	0.653	-0.50 (-27.25,26.25)	0.971	-10.40 (-37.79,16.99)	0.457
SG deep pockets: CAL	Barros 2007	0.40 (-0.69,1.49)	0.470	0.60 (-0.85,2.05)	0.417	0.20 (-0.88,1.28)	0.717
SG deep pockets: GCF volume	Barros 2007	0.35 (-0.36,1.06)	0.337	0.30 (-0.45,1.05)	0.434	0.40 (-0.54,1.34)	0.405
SG deep pockets: IFN-γ	Barros 2007	0.00 (-0.05,0.05)	1.000	0.00 (-0.08,0.08)	1.000	0.00 (-0.08,0.08)	1.000
SG deep pockets: IL-18	Barros 2007	4.85 (-8.59,18.29)	0.479	2.70 (-11.88,17.28)	0.717	7.00 (-7.72,21.72)	0.351
SG deep pockets: IL-1b	Barros 2007	1.00 (-0.35,2.35)	0.147	1.20 (-0.21,2.61)	0.095	0.80 (-1.39,2.99)	0.473
SG deep pockets: IL-4	Barros 2007	-0.95 (-1.99,0.09)	0.074	-1.00 (-2.05,0.05)	0.061	-0.90 (-2.07,0.27)	0.130
SG deep pockets: IL-6	Barros 2007	0.15 (-0.09,0.39)	0.212	0.00 (-0.36,0.36)	1.000	0.30 (0.05,0.55)	**0.018**
SG deep pockets: PPD	Barros 2007	-0.05 (-0.92,0.82)	0.911	-0.10 (-1.14,0.94)	0.850	0.00 (-0.91,0.91)	1.000
SG gingivitis: P.a.	Barros 2007	0.16 (-0.04,0.36)	0.121	0.37 (0.08,0.66)	**0.013**	-0.05 (-0.24,0.14)	0.597
SG gingivitis: Pa.m.	Barros 2007	0.05 (-0.51,0.61)	0.860	0.49 (-0.23,1.21)	0.181	-0.40 (-0.93,0.13)	0.137
SG gingivitis: Pr.m.	Barros 2007	0.49 (0.10.0.88)	**0.014**	0.97 (0.45,1.49)	**<0.001**	0.01 (-0.34,0.36)	0.955
SG gingivitis: Sta.a	Barros 2007	0.75 (0.27,1.23)	**0.002**	1.40 (0.79,2.01)	**<0.001**	0.10 (-0.43,0.63)	0.710
SG gingivitis: Str.a.	Barros 2007	0.29 (-0.01,0.59)	0.060	0.68 (0.18,1.18)	**0.007**	-0.10 (-0.25,0.05)	0.192
SG gingivitis: Str.mi.	Barros 2007	0.08 (-0.20,0.36)	0.574	0.34 (-0.08,0.76)	0.113	-0.19 (-0.38,0.00)	0.051
SG gingivitis: Str.mu.	Barros 2007	0.19 (-0.20,0.58)	0.342	0.49 (-0.17,1.15)	0.144	-0.11 (-0.36,0.14)	0.378
SG gingivitis: Tr.d.	Barros 2007	0.21 (-0.08,0.50)	0.151	0.39 (-0.09,0.87)	0.108	0.02 (-0.17,0.21)	0.833
SG non-smokers: BOP	Barros 2007	-2.80 (-9.05,3.45)	0.380	-3.40 (-10.00,3.20)	0.313	-1.80 (-8.98,5.38)	0.623

SG non-smokers: CAL	Barros 2007	0.11 (-0.12,0.34)	0.356	0.00 (-0.23,0.23)	1.000	0.30 (-0.07,0.67)	0.116
SG non-smokers: CAL>3	Barros 2007	3.07 (-3.36,9.50)	0.349	1.30 (-4.65,7.25)	0.668	6.00 (-4.79,16.79)	0.276
SG non-smokers: DMFT	Barros 2007	1.77 (-0.53,4.07)	0.131	0.90 (-1.60,3.40)	0.480	3.20 (0.29,6.11)	**0.031**
SG non-smokers: no of teeth	Barros 2007	-1.38 (-3.16,0.40)	0.128	-1.00 (-3.01,1.01)	0.330	-2.00 (-4.62,0.62)	0.135
SG non-smokers: PI	Barros 2007	-13.90 (-24.78,-3.02)	**0.012**	-14.20 (-24.97,-3.44)	**0.010**	-13.40 (-33.12,6.32)	0.183
SG non-smokers: PPD	Barros 2007	0.86 (0.72,1.00)	**<0.001**	0.90 (0.69,1.11)	**<0.001**	0.80 (0.71,0.89)	**<0.001**
SG periodontitis: B.u.	Barros 2007	0.17 (0.07,0.27)	**0.001**	0.30 (0.16,0.44)	**<0.001**	0.03 (-0.05,0.11)	0.457
SG periodontitis: C.g.	Barros 2007	0.22 (-0.06,0.50)	0.127	0.44 (0.09,0.79)	**0.014**	-0.01 (-0.30,0.28)	0.946
SG periodontitis: P.m.	Barros 2007	0.42 (-0.00,0.84)	0.052	0.86 (0.22,1.50)	**0.009**	-0.02 (-0.32,0.28)	0.896
SG periodontitis: S.ang.	Barros 2007	0.35 (0.06,0.64)	**0.018**	0.77 (0.36,1.18)	**<0.001**	-0.07 (-0.26,0.12)	0.459
SG periodontitis: S.aur.	Barros 2007	0.40 (-0.06,0.86)	0.091	0.83(0.16,1.50)	**0.015**	-0.04 (-0.39,0.31)	0.823
SG periodontitis: S.int.	Barros 2007	0.21 (0.01,0.42)	**0.044**	0.43 (0.14,0.72)	**0.004**	-0.01 (-0.18,0.16)	0.906
SG periodontitis: S.mit.	Barros 2007	0.16 (-0.06,0.38)	0.145	0.34 (0.07,0.61)	**0.012**	-0.03 (-0.23,0.17)	0.766
SG periodontitis: S.mut.	Barros 2007	0.22 (-0.13,0.57)	0.218	0.54 (0.04,1.04)	**0.033**	-0.10 (-0.37,0.17)	0.468
SG shallow pockets: CAL	Barros 2007	-0.25 (-0.37,-0.13)	**<0.001**	-0.30 (-0.46,-0.14)	**<0.001**	-0.20 (-0.36,-0.04)	**0.014**
SG shallow pockets: GCF volume	Barros 2007	0.05 (-0.50,0.60)	0.859	0.10 (-0.51,0.71)	0.748	0.00 (-0.73,0.73)	1.000
SG shallow pockets: IFN-γ	Barros 2007	0.00 (-0.05,0.05)	1.000	0.00 (-0.08,0.08)	1.000	0.00 (-0.08,0.08)	1.000
SG shallow pockets: IL-18	Barros 2007	-7.75 (-24.54,9.04)	0.365	-10.70 (-27.33,5.93)	0.207	-4.80 (-23.08,13.48)	0.607
SG shallow pockets: IL-1b	Barros 2007	-0.65 (-1.47,0.17)	0.122	-0.80 (-1.69,0.09)	0.079	-0.50 (-1.39,0.39)	0.272
SG shallow pockets: IL-6	Barros 2007	0.00 (-0.13,0.13)	1.000	0.00 (-0.00,0.00)	1.000	0.00 (-0.26,0.26)	1.000
SG shallow pockets: PI	Barros 2007	-21.60 (-44.76,1.56)	0.068	-26.00 (-54.59,2.59)	0.075	-17.20 (-43.47,9.07)	0.199
SG shallow pockets: PPD	Barros 2007	-0.25 (-0.41,-0.09)	**0.002**	-0.20 (-0.38,-0.02)	**0.032**	-0.30 (-0.53,-0.07)	**0.009**
SG smokers: BOP	Barros 2007	-5.87 (-15.93,4.19)	0.253	-7.70 (-18.38,2.98)	0.157	-4.30 (-15.22,6.62)	0.440
SG smokers: CAL	Barros 2007	-0.03 (-0.54,0.48)	0.907	-0.30 (-0.83,0.23)	0.265	0.20 (-0.35,0.75)	0.479
SG smokers: CAL>3	Barros 2007	5.19 (-9.72,20.10)	0.495	0.40 (-15.09,15.89)	0.960	9.30 (-6.60,25.20)	0.252
SG smokers: DMFT	Barros 2007	4.10 (1.38,6.82)	**0.003**	4.80 (1.67,7.93)	**0.003**	3.50 (0.51,6.49)	**0.022**
SG smokers: no of teeth	Barros 2007	-1.88 (-4.26,0.50)	0.121	0.00 (-3.19,3.19)	1.000	-3.50 (-6.01,-0.99)	**0.006**
SG smokers: PI	Barros 2007	-12.96 (-29.87,3.95)	0.133	-13.50 (-32.09,5.09)	0.155	-12.50 (-31.25,6.25)	0.191
SG smokers: PPD	Barros 2007	0.41 (0.14,0.68)	**0.003**	0.30 (-0.17,0.77)	0.210	0.50 (0.29,0.71)	**<0.001**

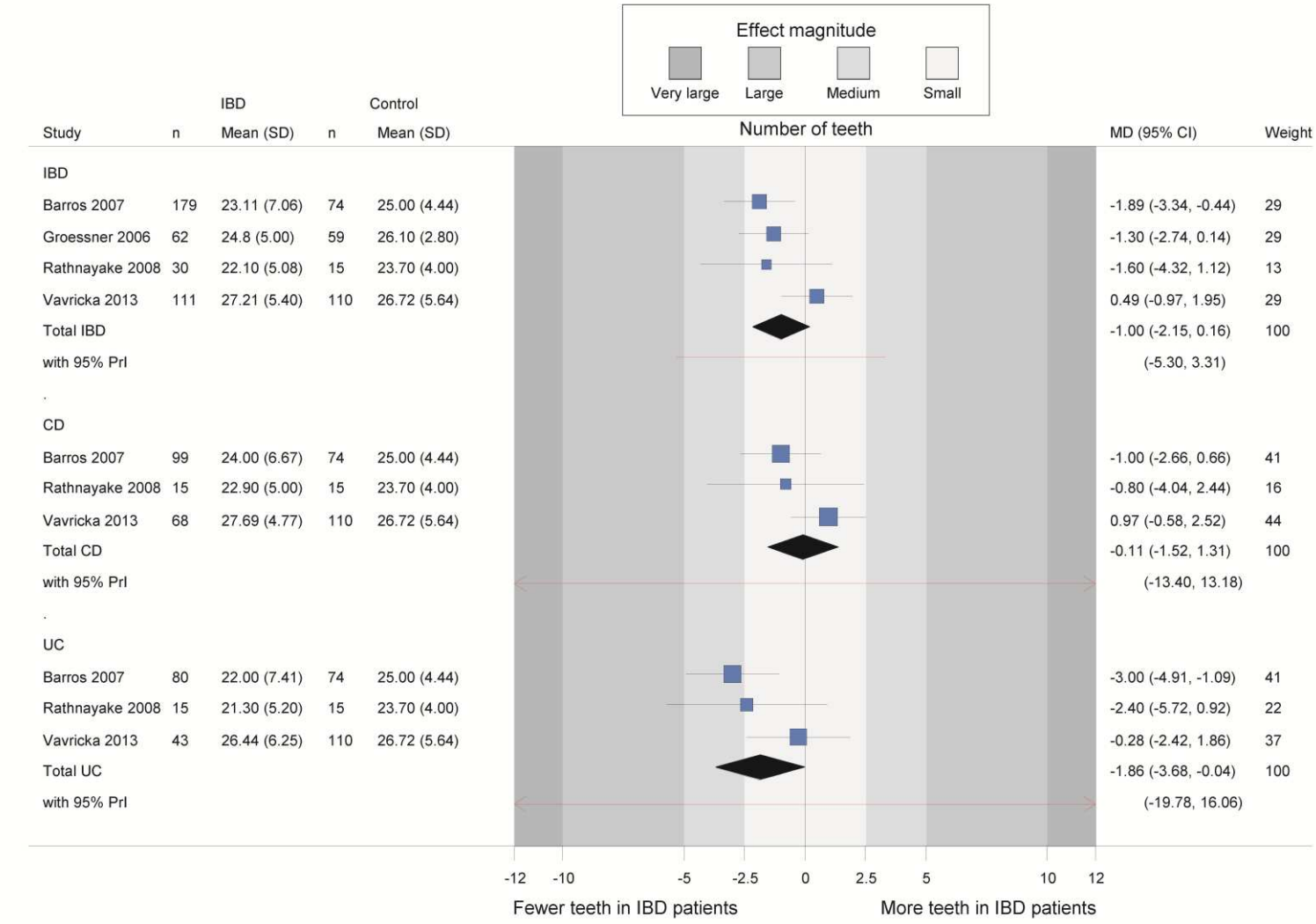
TNFα	Barros 2007	-0.82 (-2.73,1.09)	0.400	-0.30 (-2.43,1.83)	0.783	-1.30 (-3.26,0.66)	0.194
DMFS	Groessner 2006	7.60 (-2.77,17.97)	0.151	-	-	-	-
Furcation involvement	Groessner 2006	7.90 (-3.82,19.62)	0.186	-	-	-	-
CAL>4	Habasneh 2012	15.66 (10.41,20.91)	**<0.001**	12.25 (4.76,19.74)	**0.001**	17.65 (11.23,24.07)	**<0.001**
CAL>5	Habasneh 2012	3.51 (1.58,5.44)	**<0.001**	0.03 (-2.12,2.18)	0.978	5.55 (2.86,8.24)	**<0.001**
GI	Habasneh 2012	0.94 (0.77,1.11)	**<0.001**	0.88 (0.66,1.10)	**<0.001**	0.97 (0.79,1.15)	**<0.001**
GR	Habasneh 2012	0.30 (0.14,0.46)	**<0.001**	0.09 (-0.09,0.27)	0.335	0.42 (0.24,0.60)	**<0.001**
SG gingivitis: CAL	Rathnayake 2008	-0.15 (-0.31,0.01)	0.064	-0.30 (-0.50,-0.10)	**0.004**	0.00 (-0.20,0.20)	1.000
SG gingivitis: GCF	Rathnayake 2008	0.05 (-0.36,0.46)	0.809	0.10 (-0.35,0.55)	0.664	0.00 (-0.54,0.54)	1.000
SG gingivitis: PPD	Rathnayake 2008	-0.40 (-0.64,-17)	**0.001**	-0.30 (-0.54,-0.06)	**0.015**	-0.50 (-0.84,-0.17)	**0.003**
SG gingivitis: VPI	Rathnayake 2008	-45.00 (-75.18,-14.82)	**0.003**	-50.00 (-91.91,-8.09)	**0.019**	-40.00 (-75.37,-4.64)	**0.027**
SG periodontitis: CAL	Rathnayake 2008	0.85 (0.14,1.56)	**0.019**	0.70 (-0.41,1.81)	0.216	1.00 (0.36,1.64)	**0.002**
SG periodontitis: GCF	Rathnayake 2008	0.35 (-0.18,0.88)	0.194	0.30 (-0.26,0.86)	0.290	0.40 (-0.30,1.10)	0.260
SG periodontitis: PPD	Rathnayake 2008	0.20 (-0.27,0.67)	0.406	0.20 (-0.44,0.84)	0.538	0.20 (-0.37,0.77)	0.492
SG periodontitis: VPI	Rathnayake 2008	-11.65 (-46.29,22.99)	0.510	-8.30 (-48.06,31.46)	0.682	-15.00 (-56.11,26.11)	0.475
D(ecayed) index	Slebioda 2011	1.57 (0.91,2.23)	**<0.001**	1.70 (0.90,2.50)	**<0.001**	1.20 (0.31,2.09)	**0.008**
Dental caries treatment index	Slebioda 2011	-0.15 (-0.24,-0.06)	**0.002**	-0.18 (-0.28,-0.08)	**0.000**	-0.08 (-0.23,0.07)	0.308
Fillings	Slebioda 2011	-0.20 (-1.57,1.17)	0.775	-0.20 (-1.67,1.27)	0.790	-0.20 (-2.24,1.84)	0.848
M(issing) index	Slebioda 2011	5.37 (3.41,7.33)	**<0.001**	5.40 (3.16,7.65)	**<0.001**	5.30 (1.81,8.79)	**0.003**
Oral hygiene index	Slebioda 2011	1.24 (0.99,1.49)	**<0.001**	1.40 (1.14,1.66)	**<0.001**	0.80 (0.41,1.19)	**<0.001**
Bleeding in deepest tooth	Vavricka 2013	0.12 (0.03,0.21)	**0.012**	0.16 (0.04,0.28)	**0.008**	0.05 (-0.07,0.17)	0.406
CAL in deepest tooth	Vavricka 2013	0.43 (0.11,0.75)	**0.009**	0.43 (0.04,0.83)	**0.033**	0.44 (-0.01,0.89)	0.055
Papilla bleeding index	Vavricka 2013	0.23 (0.12,0.34)	**<0.001**	0.23 (0.11,0.35)	**<0.001**	0.22 (0.03,0.41)	**0.023**
Outcome	**Study**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
CAL>4	Groessner 2006	2.30 (1.01,5.26)	**0.048**	-	-	-	-
CAL>5	Groessner 2006	2.01 (0.97,4.16)	0.060	-	-	-	-
Dentine caries	Groessner 2006	2.39 (1.08,5.31)	**0.032**	-	-	-	-
Atrophic tongue	Slebioda 2011	13.70 (0.78,241.42)	0.074	19.18 (1.09,339.03)	**0.044**	-	-

Candida	Slebioda 2011	3.09 (1.62,5.87)	**0.001**	3.24 (1.62,6.47)	**0.001**	2.70 (1.06,6.90)	**0.038**
Candida +	Slebioda 2011	0.98 (0.46,2.08)	0.953	0.84 (0.37,1.92)	0.673	1.43 (0.50,4.05)	0.505
Candida ++	Slebioda 2011	1.30 (0.48,3.50)	0.601	1.68 (0.61,4.62)	0.316	0.38 (0.04,3.21)	0.371
Candida +++	Slebioda 2011	7.13 (2.05,24.86)	**0.002**	6.62 (1.83,23.90)	**0.004**	8.69 (2.04,36.99)	**0.003**
Candida wz	Slebioda 2011	8.57 (0.47,157.58)	0.148	11.84 (0.64,218.33)	0.097	-	-
Complete dentition	Slebioda 2011	0.18 (0.09,0.35)	**<0.001**	0.19 (0.09,0.39)	**<0.001**	0.15 (0.05,0.44)	**0.001**
CPITN 2-3	Slebioda 2011	4.10 (2.13,7.89)	**<0.001**	4.20 (2.07,8.52)	**<0.001**	3.83 (1.45,10.11)	**0.007**
CPITN 0-1	Slebioda 2011	0.18 (0.09,0.35)	**<0.001**	0.15 (0.07,0.32)	**<0.001**	0.26 (0.10,0.69)	**0.007**
Dark indelible patches	Slebioda 2011	0.48 (0.08,2.95)	0.429	0.32 (0.03,3.19)	0.334	0.93 (0.09,9.38)	0.951
Deaquamative cheilitis	Slebioda 2011	1.11 (0.18,6.82)	0.911	1.00 (0.14,7.31)	1.000	1.42 (0.12,16.34)	0.780
Edentia	Slebioda 2011	6.93 (0.37,130.94)	0.196	9.54 (0.50,180.64)	0.133	-	-
Fissured tongue	Slebioda 2011	3.03 (0.33,27.75)	0.326	3.09 (0.31,30.45)	0.334	2.88 (0.17,47.78)	0.461
Fordyce's spots	Slebioda 2011	1.31 (0.37,4.67)	0.675	1.00 (0.24,4.17)	1.000	2.25 (0.47,10.85)	0.312
Geographic tongue	Slebioda 2011	1.89 (0.36,10.03)	0.455	2.06 (0.37,11.63)	0.413	1.42 (0.12,16.34)	0.780
Linea alba	Slebioda 2011	0.19 (0.09,0.40)	**<0.001**	0.20 (0.09,0.45)	**<0.001**	0.16 (0.04,0.59)	**0.006**
Palatal erythema	Slebioda 2011	2.05 (0.53,8.04)	0.301	2.88 (0.73,11.35)	0.130	0.38 (0.02,7.58)	0.525
Palatal papillary hyperplasia	Slebioda 2011	2.24 (0.09,55.76)	0.623	3.04 (0.12,75.99)	0.498	-	-
Recurrent aphthous stomatitis	Slebioda 2011	4.24 (1.64,10.93)	**0.003**	3.97 (1.48,10.68)	**0.006**	5.02 (1.53,16.43)	**0.008**
Recurrent labial herpes	Slebioda 2011	0.36 (0.06,1.99)	0.240	0.49 (0.09,2.74)	0.413	0.29 (0.02,5.58)	0.412
Rhomboid glossitis	Slebioda 2011	6.93 (0.37,130.94)	0.196	9.54 (0.50,180.64)	0.133	-	-
Sound teeth	Slebioda 2011	0.31 (0.16,0.59)	**<0.001**	0.27 (0.14,0.55)	**<0.001**	0.42 (0.17,1.08)	0.071
Swollen buccal mucosa	Slebioda 2011	7.98 (2.30,27.66)	**0.001**	10.24 (2.90,36.16)	**<0.001**	3.05 (0.57,16.20)	0.192
Teeth with radicular or coronal decay	Slebioda 2011	3.27 (1.71,6.27)	**<0.001**	3.69 (1.83,7.43)	**<0.001**	2.36 (0.93,6.01)	0.071
White coated tongue	Slebioda 2011	1.62 (0.87,3.03)	0.132	1.50 (0.77,2.95)	0.234	2.01 (0.77,5.25)	0.156
White indelible patches and plates	Slebioda 2011	3.83 (0.44,33.57)	0.225	1.00 (0.06,16.31)	1.000	13.14 (1.39,124.09)	**0.025**
Buccal swelling	Zervou 2004	4.83 (0.19,122.53)	0.340	9.83 (0.38,254.52)	0.169	-	-
Buccal trauma	Zervou 2004	41.98 (2.34,754.61)	**0.011**	65.00 (3.37,1253.85)	**0.006**	26.60 (1.29,549.44)	**0.034**
Cobblestoning	Zervou 2004	12.09 (0.60,242.89)	0.103	26.60 (1.29,549.44)	**0.034**	-	-
Erythema migrans	Zervou 2004	4.83 (0.19,122.53)	0.340	9.83 (0.38,254.52)	0.169	-	-

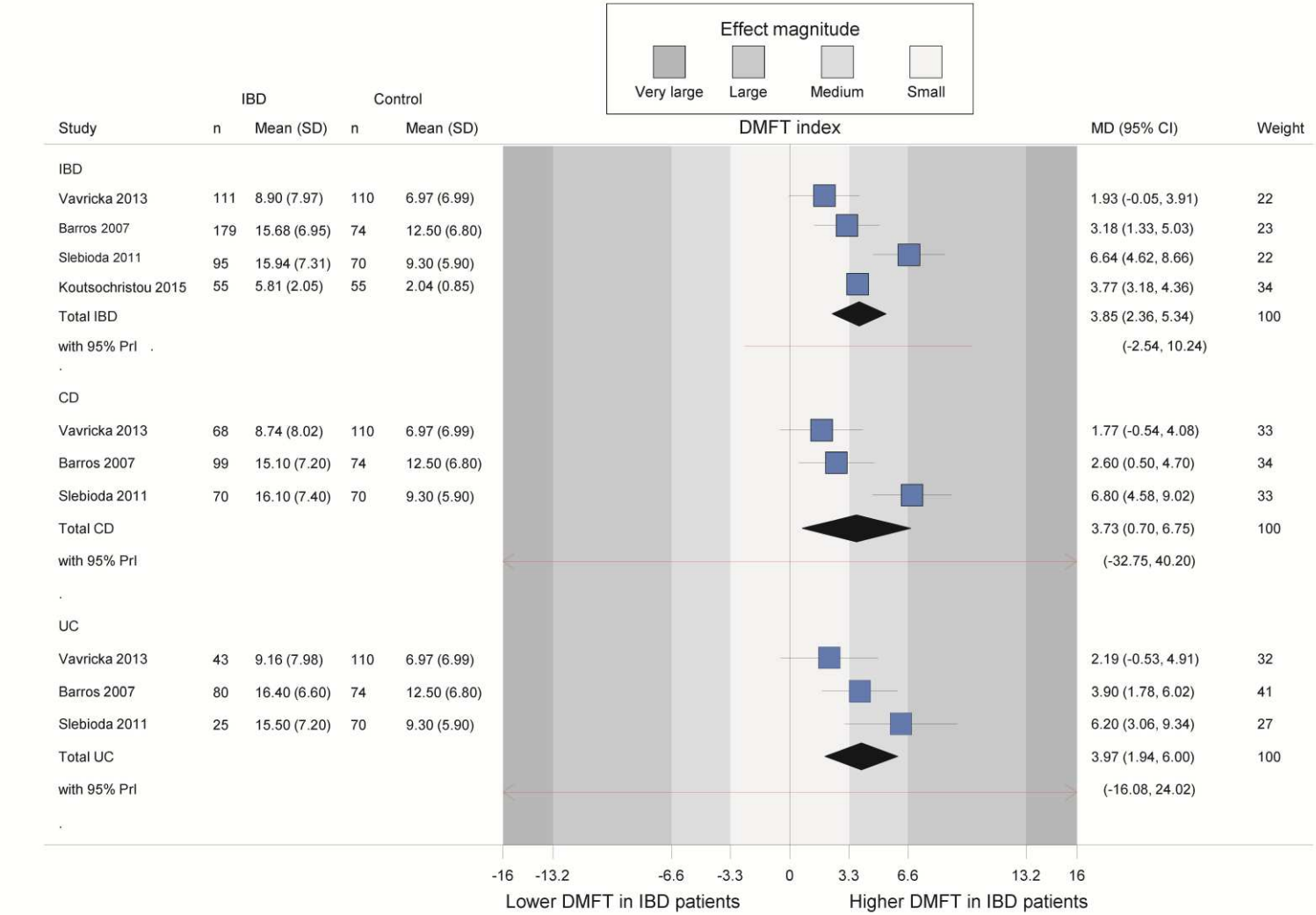
Fissures elsewhere	Zervou 2004	12.09 (0.60,242.89)	0.103	26.60 (1.29,549.44)	**0.034**	-	-
Fissures lip	Zervou 2004	0.33 (0.10,1.11)	0.073	0.33 (0.07,1.64)	0.175	0.33 (0.07,1.64)	0.175
Fissures medline	Zervou 2004	0.14 (0.03,0.66)	**0.013**	0.30 (0.06,1.49)	0.140	0.06 (0.00,1.10)	0.058
Gingival bleeding	Zervou 2004	16.13 (0.84,311.36)	0.066	37.17 (1.87,740.64)	**0.018**	-	-
Gingivitis	Zervou 2004	16.13 (0.84,311.36)	0.066	26.60 (1.29,549.44)	**0.034**	9.83 (0.38,254.52)	0.169
Leukoplakia	Zervou 2004	4.83 (0.19,122.53)	0.340	9.83 (0.38,254.52)	0.169	-	-
Lip swelling	Zervou 2004	16.13 (0.84,311.36)	0.066	26.60 (1.29,549.44)	**0.034**	9.83 (0.38,254.52)	0.169
Lymphadenopathy	Zervou 2004	48.66 (2.72,870.23)	**0.008**	83.82 (4.37,1 608.44)	**0.003**	26.60 (1.29,549.44)	**0.034**
Polypoid tags	Zervou 2004	12.09 (0.60,242.89)	0.103	26.60 (1.29,549.44)	**0.034**	-	-
Salivary gland involvement	Zervou 2004	16.13 (0.84,311.36)	0.066	-	-	37.17 (1.87,740.64)	**0.018**

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MD, mean difference; CI, confidence interval; SG, subgroup; IL, interleukin; IFN, interferon; PI, plaque index; CAL, clinical attachment level; GCF; gingival crevicular fluid; PPD, pocket probing depth; P.a., Peptostreptococcus anaerobius; Pa.m., Parvimonas micra; Pr.m., Prevotella melaninogenica; Sta.a., Staphylococcus aureus; Str.a., Streptococcus anginosus; Str.mi., Streptococcus mitis; Str.mu., Streptococcus mutans; Tr.d., Treponema denticola; BOP, bleeding on probing; DMFT, decayed missing filled teeth; B.u., Bacteroides ureolyticus; C.g., Campylobacter gracilis; P.m., P. melaninogenica; S.ang., S. anginosus; S.aur., S. aureus; S.int., S. intermedius; S.mit., S. mitis; S.mut., S. mutans; TNF, tumor necrosis factor; DMFS, decayed missing filled tooth surfaces; GI, gingival index; GR, gingival recession; VPI, visible plaque index; OR, odds ratio; CPITN, community periodontal index treatment need.

Appendix S5. Forest plot with the meta-analyses regarding the number of teeth. IBD, inflammatory bowel disease; n, sample; SD, standard deviation; MD, mean difference; CI, confidence interval; PrI, predictive interval; CD, Crohn's disease; UC, ulcerative colitis.



Appendix S6. Forest plot with the meta-analyses regarding the DMFT index. DMFT, decayed missing filled teeth; IBD, inflammatory bowel disease; n, sample; SD, standard deviation; MD, mean difference; CI, confidence interval; PrI, predictive interval; CD, Crohn's disease; UC, ulcerative colitis.



Appendix S7. Results of Meta-Analyses Comparing Patients With Crohn's Disease Compared to Healthy Patients

		Effect size				Heterogeneity	
Outcome	Studies	MD or OR (95% CI)	p	95% PrI		I^2 (95% CI)	τ^2
Primary outcome							
Periodontitis	4	OR: 3.96 (2.39,6.54)	**<0.001**	1.31,11.92		0 (0,68)	0
Secondary outcomes							
Number of teeth	3	MD: -0.11 (-1.52,1.31)	0.881	-13.40,13.18		36 (0,82)	0.572
DMFT index	3*	MD: 3.73 (0.70,6.75)	**0.016**	-32.75,40.20		82 (0,92)	5.863
Plaque index	[c]						
Bleeding on probing	[a]						
Clinical attachment loss	[b]						
Clinical attachment loss > 3mm	2	MD: 2.42 (-2.49,7.33)	0.333	NA		0 (NA)	0
Pocket probing depth	3*	MD: 0.56 (-0.01,1.13)	0.054	-6.67,7.79		95 (90,97)	0.239
Pocket probing depth > 3mm	2	MD: 4.82 (0.65,8.99)	**0.024**	NA		0 (NA)	0
Pocket probing depth > 4mm	3*	MD: -3.49 (-9.41,2.43)	0.248	-73.87,66.89		90 (67,95)	21.550
Oral lesions	2*	OR: 5.17 (0.53,50.58)	0.158	NA		96 (NA)	2.590
Angular cheilitis	2	OR: 10.04 (0.85,118.26)	0.067	NA		56 (NA)	1.877
Aphthous lesions	2	OR: 1.99 (0.56,7.08)	0.289	NA		74 (NA)	0.626
Hairy tongue	2	OR: 9.44 (1.07,83.01)	**0.043**	NA		0 (NA)	0
Ulceration	2	OR: 11.16 (1.30,95.55)	**0.028**	NA		0 (NA)	0

MD, mean difference; OR, odds ratio; CI, confidence interval; PrI, predictive interval; NA, not applicable; DMFT, decayed missing filling teeth.
*extreme heterogeneity, but agrees on direction; effect magnitude might be misestimated.
[a] Meta-analysis omitted; three studies with extreme heterogeneity; studies evenly distributed (MD=1.65; 95% CI=-7.06,10.37; p=0.710; I^2=77)
[b] Meta-analysis omitted; three studies with extreme heterogeneity; studies evenly distributed (MD=0.013; 95% CI=-0.42,0.45; p=0.954; I^2=78)
[c] Meta-analysis omitted; three studies with extreme heterogeneity; studies evenly distributed (Standardized Mean Difference=-0.05; 95% CI=-0.77,0.67; p=0.891; I^2=90)

Appendix S8. Results of Meta-Analyses Comparing Patients With Ulcerative Colitis Compared to Healthy Patients

		Effect size				Heterogeneity	
Outcome	Studies	MD or OR (95% CI)	p	95% PrI		I^2 (95% CI)	τ^2
Primary outcome							
Periodontitis	3	OR: 5.11 (2.92,8.92)	**<0.001**	0.14,189.85		0 (0,73)	0
Secondary outcomes							
Number of teeth	3	MD: -1.86 (-3.68,-0.04)	**0.045**	-19.78,16.06		44 (0,83)	1.128
DMFT index	3	MD: 3.97 (1.94,6.00)	**<0.001**	-16.08,24.04		44 (0,83)	1.420
Plaque index	2[a,*]	MD: 0.50 (-0.42,1.41)	0.289	NA		95 (NA)	0.415
Bleeding on probing	3	MD: 1.42 (-5.01,7.86)	0.665	-69.58,72.43		67 (0,88)	20.444
Clinical attachment loss	3	MD: 0.40 (-0.02,0.828)	0.061	-4.40,5.21		74 (0,90)	0.096
Clinical attachment loss > 3mm	2	MD: 13.68 (7.29,20.08)	**<0.001**	NA		7 (NA)	1.515
Pocket probing depth	3*	MD: 0.66 (0.27,1.05)	**0.001**	-4.22,5.54		96 (91,97)	0.108
Pocket probing depth > 3mm	2	MD: 0.55 (-10.43,11.54)	0.921	NA		64 (NA)	44.715
Pocket probing depth > 4mm	[b]						
Oral lesions	2*	OR: 6.27 (1.53,25.70)	**0.011**	NA		87 (NA)	0.906
Angular cheilitis	2	OR: 4.54 (0.07,288.50)	0.476	NA		73 (NA)	6.588
Aphthous lesions	3	OR: 3.38 (1.75,6.53)	<0.001	0.05,242.46		0 (0,73)	0
Hairy tongue	2	OR: 9.21 (0.93,91.25)	0.058	NA		0 (NA)	0
Ulceration	2	OR: 9.21 (0.93,91.25)	0.058	NA		0 (NA)	0

MD, mean difference; OR, odds ratio; CI, confidence interval; PrI, predictive interval; NA, not applicable; DMFT, decayed missing filling teeth.
*extreme heterogeneity, but agrees on direction; effect magnitude might be misestimated.
[a] Omitted study of Rathnayake 2008 to achieve homogeneity (Standardized Mean Difference (SMD) =0.29; 95% CI=-0.47,1.04; p=0.460; I^2=91); used SMD to combine two plaque indeces
[b] Meta-analysis omitted; three studies with extreme heterogeneity; studies evenly distributed (MD=-1.73; 95% CI=-5.78,2.33; p=0.404; I^2=75)

Appendix S9. Additional details about the Summary of Findings table (Table 4).

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large Effect	Dose Response	Residual Confounding
Periodontitis IBD	No serious limitations	Little to no heterogeneity; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	Rated up by two levels for very large effect included in the confidence and predictive interval.	No reason to rate up	Rated up by one; estimates adjusted for confounders confirmed results agree with original analyses.
Periodontitis CD	No serious limitations	Little to no heterogeneity; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	Rated up by one level for large effect included in the confidence and predictive interval.	No reason to rate up	Rated up by one; estimates adjusted for confounders confirmed results agree with original analyses.
Periodontitis UC	No serious limitations	Little to no heterogeneity; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	Rated up by two levels for very large effect included in the confidence and predictive interval.	No reason to rate up	Rated up by one; estimates adjusted for confounders confirmed results agree with original analyses.
No of teeth IBD	No serious limitations	Little to no heterogeneity; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	No reason to rate up	No reason to rate up	No reason to rate up
No of teeth CD	No serious limitations	Little to no heterogeneity; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	No reason to rate up	No reason to rate up	No reason to rate up
No of teeth UC	No serious limitations	Little to no heterogeneity; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	No reason to rate up	No reason to rate up	No reason to rate up
DMFT IBD	No serious limitations	Extreme heterogeneity; however effects agree in direction and confidence regarding decision is unaffected; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	No reason to rate up	No reason to rate up	No reason to rate up
DMFT CD	No serious limitations	Extreme heterogeneity; however effects agree in direction and confidence regarding decision is unaffected; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	No reason to rate up	No reason to rate up	No reason to rate up
DMFT UC	No serious limitations	Little to no heterogeneity; no apparent reason to downgrade.	Directly relevant; no apparent reason to downgrade.	Adequate sample; no apparent reason to downgrade.	Small number of studies precluded formal assessment of reporting bias; no apparent reason to downgrade.	No reason to rate up	No reason to rate up	No reason to rate up

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; DMFT, decayed-missing-filled-teeth index.

Appendix S10. Exploratory comparison of differences between UC and CD patients (UC minus CD).

		Effect size				**Heterogeneity**	
Outcome	**Studies**	**MD or OR (95% CI)**	**P**	**95% PrI**		**I^2 (95% CI)**	**τ^2**
Primary outcome							
Periodontitis	2	OR: 0.86 (0.11,6.58)	0.884	NA		44 (NA)	1.129
Secondary outcomes							
Number of teeth	4	MD: -1.67 (-2.97,-0.34)	**0.013**	-10.68,7.41		0 (0,73)	0
DMFT index	3	MD: 0.69 (-0.81,2.20)	0.365	-9.05,10.44		0 (0,73)	0
Plaque index	3	SMD: 0.33 (0.13,0.54)	**0.002**	-1.02,1.69		0 (0,73)	0
Bleeding on probing	3	MD: 0.41 (-2.91,3.72)	0.811	-21.09,21.90		0 (0,73)	0
Clinical attachment loss	3	MD: 0.40 (0.20,0.59)	**<0.001**	-0.89,1.68		0 (0,73)	0
Clinical attachment loss > 3mm	2	MD: 10.18 (4.10,16.25)	**<0.001**	NA		0 (0,73)	0
Pocket probing depth	3	MD: 0.12 (-0.03,0.28)	0.124	-1.33,1.58		33 (0,81)	0.001
Pocket probing depth > 3mm	*						
Pocket probing depth > 4mm	3	MD: 1.33 (-0.80,3.45)	0.220	-21.64,24.30		69 (0,89)	2.092
Angular cheilitis	2	OR: 0.52 (0.13,2.07)	0.354	NA		0 (NA)	0
Aphthous lesions	3	OR: 1.86 (0.97,3.58)	0.063	0.03,129.72		0 (0,73)	0
Hairy tongue	2	OR: 0.82 (0.14,4.76)	0.829	NA		0 (NA)	0
Ulceration	2	OR: 0.68 (0.12,3.71)	0.653	NA		0 (NA)	0

UC, ulcerative colitis; CD, Crohn's disease; MD, mean difference; OR, odds ratio; CI, confidence interval; PrI, predictive interval; NA, not applicable; DMFT, decayed missing filling teeth.

* Meta-analysis omitted; two studies with extreme heterogeneity; studies evenly distributed (MD=-0.59; 95% CI=-18.56,17.37; P=0.949; I^2=88)

Appendix S11. Results of random-effects meta-regression according to patient characteristics.

	Age			Sex			Smokers			Active disease			Medication use		
	n	Coefficient (95%CI)	P	n	Coefficient (95%CI)	P	n	Coefficient (95%CI)	P	n	Coefficient (95%CI)	P	n	Coefficient (95%CI)	P
Periodontitis	3	-0.66 (-18.59,17.26)	0.720	3	0.43 (-6.93,7.78)	0.594	3	1.59 (-19.73,22.91)	0.517	-	-	-	3	-0.54 (-32.66,31.58)	0.867
No of teeth	4	0.01 (-2.61,2.62)	0.992	4	2.66 (-2.41,7.74)	0.152	4	6.15 (-9.18,21.47)	0.226	3	3.50 (-93.22,100.22)	0.726	4	-7.94 (-23.40,7.52)	0.158
DMFT	3	-1.14 (-6.34,4.06)	0.219	3	0.88 (-68.93,70.70)	0.898	-	-	-	-	-	-	-	-	-

n, sample; CI, confidence interval; DMFT, decayed missing filled teeth index.

Appendix S12. Sensitivity analysis according to the periodontitis definition.

Study	Definition of periodontitis
Barros 2007	"Periodontitis was defined as the presence of at least four sites in different teeth with CAL ≥ 3 mm."
Vavricka 2013	"Crude differences regarding risk factors for periodontitis, assessed by the oral health markers LA-PPD for periodontitis…"
Habasneh 2012	"Periodontitis was defined as presence of four or more teeth with one site or more having a probing pocket depth ≥ 4 mm and clinical attachment level ≥ 3 mm."
Zervou 2004	No definition given.

	IBD		CD		UC	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Original	4.55 (3.00,6.91)	<0.001	3.96 (2.39,6.54)	<0.001	5.11 (2.92,8.92)	<0.001
Sensitivity analysis	6.07 (2.96)	<0.001	4.82 (2.88,8.08)	<0.001	3.70 (1.89,7.24)	<0.001

CAL, clinical attachment loss; LA-PPD, loss of attachment at sites with maximal periodontal pocket depth; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio.

Appendix S13. Criteria used to diagnose Inflammatory Bowel Disease (IBD), Crohn's Disease (CD), and Ulcerative Colitis (UC).

Nr.	Study	Diagnosis
1	Barros 2007	The diagnosis of CD or UC had been established previously by clinical, radiological, endoscopic and histological analyses.
2	Groessner-Schreiber 2006	The diagnosis of either CD or UC was confirmed by previously established clinical, radiological and endoscopic criteria (type of lesions, distribution*), and histological findings also had to be confirmative or compatible with this diagnosis.
3	Habashneh 2012	The diagnosis of IBD was established by clinical, radiological, endoscopic and histological criteria.
4	Koutsochristou 2015	The diagnosis of CD or UC was established according to the Porto criteria.34
~~4~~ 5	Rathnayake 2008	The diagnosis of either Crohn's disease (CD) or Ulcerative colitis (UC) was conformed by clinical, radiographic and endoscopic criteria.
~~5~~ 6	Slebioda 2011	Not specified.
~~6~~ 7	Van Dyke 1986	IBD patients were defined as those exhibiting a combination of symptoms, including diarrhea, abdominal pain, bleeding, weight loss, perianal disease, and arthritis.
~~7~~ 8	Vavricka 2013	The diagnosis of CD or UC had been established previously by clinical, radiological, endoscopic, and histological analyses.
~~8~~ 9	Zervou 2007	Not specified.

*Based on Truelove, S. C. & Pena, A. S. (1976) Course and prognosis of Crohn's disease. Gut 17, 192–201 & Lennard-Jones, J. E. (1989) Classification of inflammatory bowel disease. Scandinavian Journal of Gastroenterology 170 (Suppl.), 2–6.

Appendix S14. Additional review data

Author Contributions

SNP designed the protocol/datasheets, registered the review, designed and performed the literature searches, extracted search results, performed study screening, performed study selection, extracted data from studies, performed study quality assessment, performed statistical analysis, graded the quality of evidence with the GRADE approach, wrote first draft of the manuscript, checked and approved all data prior to submission, submitted the paper, and is responsible for the accuracy of the results.

MH checked the protocol/datasheets, performed study selection, extracted data from studies, performed study quality assessment, aided in the interpretation of the analyses, contributed to manuscript writing, checked and approved all data prior to submission

AVBN aided in the interpretation of the analyses, contributed to manuscript writing, checked and approved all data prior to submission

AF aided in the interpretation of the analyses, contributed to manuscript writing, checked and approved all data prior to submission

JD conceived the experiment, checked the protocol/datasheets, resolved conflict during the duplicate procedures, aided in the interpretation of the analyses, contributed to manuscript writing, checked and approved all data prior to submission, and is the corresponding author.

Changes to the protocol after initiation

1. The primary outcome remained the one that was pre-specified; the secondary outcomes were decided upon post hoc evaluation of all identified outcomes (giving priority to outcomes reported by most studies). As such the title
2. The SMD was used for one meta-analysis instead of the MD that was originally planned, in order to combine two similar plaque indeces.
3. Many additional outcomes (periodontal progression and response to periodontal treatment), as well as analyses (subgroup analyses, reporting bias, sensitivity analyses) were either not possible or partly possible to conduct, due to the number and nature of the included studies.
4. According to bullet's 1 and 3, the scope and title of the review was changed from a periodontitis-based one to a more general oral-health-related one, although as stated in bullet 1, the primary outcome remained as pre-specified.

5. After peer review, the literature searches were updated in January 2017 and the results from the new searches were integrated in the revised submission.